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POSTMARKETING SURVEILLANCE OF PRESCRIPTION DRUGS

NOVEMBER 1982

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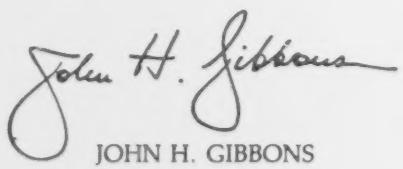
Foreword

Before a drug can be prescribed for use in the United States, it must meet minimum statutory requirements for proof of its efficacy and safety as these have been established by the U.S. Food and Drug Administration (FDA). In premarketing testing, the numbers and types of patients exposed to a drug are necessarily limited compared with the numbers and types of patients who will eventually be prescribed the drug after it is marketed. New uses, contraindications, and side effects of drugs will then inevitably be discovered. Thus, various kinds of postmarketing surveillance have been proposed over the past decade.

A background paper on postmarketing surveillance of prescription drugs was originally being prepared by the Office of Technology Assessment for the project on strategies for medical technology assessment, as requested by the House Committee on Energy and Commerce and its Subcommittee on Health and the Environment. At the further request of that committee and its subcommittee, that background paper was expanded into this full report, *Postmarketing Surveillance of Prescription Drugs*.

Current interest in drug regulation is also focused on the premarketing approval process, because the process has been criticized as unnecessarily delaying the release of valuable drugs in this country. As a result of such criticism, efforts are underway to shorten the approval process through administrative changes within FDA's Office of Drugs, and through revisions of the regulatory interpretations of the statutory requirements for "adequate tests" of a drug's safety and "substantial evidence" of its effectiveness.

This report describes the drug approval process, the history and objectives of postmarketing surveillance, the methods employed to accomplish it, and current activities in postmarketing surveillance. The report provides guidelines to determine whether shortening the drug approval process by various means would diminish its ability to detect adverse drug reactions prior to a drug's release for marketing. The report also identifies oversight issues and options for increased postmarketing surveillance both in the case that Congress decides to relax premarket approval requirements and in the case that it does not.



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Glossary of Acronyms

ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration (PHS)
ANDA	abbreviated new drug application
ADR	adverse drug reaction
CDC	Centers for Disease Control
CDS	Center for Drug Surveillance
CFR	Code of Federal Regulations
DEA	Drug Enforcement Agency
DES	diethylstilbestrol
DHHS	Department of Health and Human Services
DRA	drug regulatory authority
ETIP	Experimental Technology Incentives Program (NBS)
FDA	Food and Drug Administration
HMO	health maintenance organization
IND	investigational new drug
NBS	National Bureau of Standards (Department of Commerce)
NCHS	National Center for Health Statistics (DHHS)
NCI	National Cancer Institute (NIH)
NDA	new drug application
NIDA	National Institute on Drug Abuse (ADAMHA)
NIH	National Institutes of Health (DHHS)
NHLBI	National Heart, Lung, and Blood Institute (NIH)
PHS	Public Health Service (DHHS)
PMS	postmarketing surveillance
SOAR	screening of adverse reactions (method)
U.S.C.	United States Code
WHO	World Health Organization

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1.
Summary

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1. Summary

INTRODUCTION

To market a drug, the manufacturer must provide evidence of its efficacy and safety to the U.S. Food and Drug Administration (FDA). Once these premarketing requirements are met and the drug has been released, FDA can remove a drug from the market—after giving due notice and an opportunity for a hearing—because of new evidence on the drug's efficacy and safety, the discovery that the drug was approved on the basis of any untrue statement of a material fact, or the failure of the drug to meet manufacturing standards. In cases where a drug may be an "imminent hazard to the public health," FDA can suspend the drug's approval immediately, giving prompt notice of the action and offering the opportunity for an expedited hearing.

In premarketing testing, the numbers and types of patients used to demonstrate a drug's efficacy and safety are limited compared with the numbers and types of patients who will eventually be prescribed the drug after it is marketed. The initial decision to approve a drug for use, however, must be made on the basis of the available knowledge.

Although postmarketing surveillance cannot provide knowledge of the safety or efficacy of drugs at the time of their introduction on the market, **various kinds of postmarketing surveillance have been proposed over the past decade to monitor and aid in modifying the use of drugs. The principal focus of postmarketing surveillance proposals has been on the safe use of prescription drugs,** even though the range of issues has encompassed both efficacy and safety considerations, e.g., concern over refinements in use as well as better definition of drug risks.

Current interest in prescription drug evaluation and monitoring is focused on the premarketing approval process and the length of time it takes for a drug to be approved by FDA; postmarketing surveillance appears to have waned as a policy issue. Thus, policy formulation and implementation for the premarketing approval process is being pursued without parallel efforts for the postmarketing period.

However, postmarketing surveillance deserves attention as a policy issue for both short- and long-term objectives. Regarding short-term action, if current testing requirements for the premarketing approval process are reduced, pharmaceutical manufacturers could be required to maintain their drug evaluation responsibilities by increasing postmarketing surveillance. Regarding long-term action, postmarketing surveillance remains a policy issue irrespective of current interest in the premarketing approval process: it is only after marketing that a drug's full therapeutic and harmful potentials can be determined.

One way to shorten the premarketing period of the drug approval process would be by reinterpreting the regulations for assessing safety and efficacy. This report provides theoretical and experiential criteria for evaluating how such changes may affect the ability of current guidelines to detect a drug's harmful and beneficial effects. It also discusses the kinds of qualitative changes in the evidence required for drug approval that FDA is implementing. Finally, the report identifies options relating to FDA's postmarketing surveillance. These options could be implemented regardless of whether there is a change in current premarketing drug approval requirements.

THE DRUG APPROVAL PROCESS

A drug's sponsor must provide: 1) "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested;" and 2) "substantial evidence that the drug will have the effect it purports or is represented to have" (21 U.S.C., sec. 355 (d)). This statutory language has led in practice to FDA's establishing a premarketing phase of drug testing that consists of two parts: 1) the investigational new drug (IND) application process, and 2) the filing of a new drug application (NDA).

The IND application describes the investigators' qualifications and the planned clinical trials, the chemical composition of the drug, and data on the pharmacology and toxicology of the new drug collected in animal studies and in prior human studies, if any, such as those conducted in other countries.

The clinical investigations in the IND process are divided into three phases (24):

- *Phase I: Clinical Pharmacology* is that phase in which a drug is first used on humans to confirm dose ranges and pharmacologic effect. The number of subjects in phase I varies depending on the drug, but is usually in the range of 20 to 80 (excluding control patients). Pharmacodynamic and metabolic studies, in whichever stage of investigation they are performed, are considered to be phase I clinical pharmacologic studies.
- *Phase II: Clinical Investigation* consists of controlled clinical trials to demonstrate a drug's effectiveness and relative safety. These are performed on closely monitored patients of limited number, usually 100 to 200 patients, with equal numbers of control patients.
- *Phase III: Clinical Trials* are expanded controlled and uncontrolled trials to gather additional evidence of a drug's effectiveness for specific indications and to more precisely define its adverse effects. Phase III studies observe a total of 500 to 3,000 patients in more natural settings—in clinics, outpatient hospital facilities, and private practice. Phase III usually consists of more than two controlled trials.

After completion of the testing required under the IND application, the sponsor may file an NDA. At least two well-controlled studies establishing each indication for which the drug is intended are required. More than one indication can be established in a single study. (These requirements are under review; see chs. 3 and 6.)

All INDs are classified by chemical type and therapeutic potential, so that those drugs considered by FDA to be of particular therapeutic importance can receive priority review. The highest classification is given to drugs that are new molecular entities (type 1) and that may represent important therapeutic gains (type A)—type 1A drugs.

Several mechanisms are available to FDA to obtain information about drugs once they have been approved for marketing. Once the NDA has been approved, the sponsor is required to monitor information and submit reports about the drug. Other information on adverse drug reactions (ADRs) is monitored by FDA in a number of ways:

- the Spontaneous Reaction Reporting Program, in which information on ADRs is sent to FDA by physicians, pharmacists, and hospitals;
- a monthly review of the medical literature on ADRs (reports and letters to the editors of medical journals, etc.);
- intensive surveillance and epidemiologic studies of ADRs in selected hospitalized and ambulatory populations;
- several specialized registries that collect and analyze possible ADRs;
- in-house monitoring and research studies of such data bases as those of the Medicaid Medical Information Systems of some States and those of commercial sources of drug use data; and
- the World Health Organization, which exchanges reports with FDA, each summarizing the ADRs added to their systems in the previous year.

This postmarketing information is useful for two purposes. First, it may provide the grounds for FDA to remove a drug from the market, when such action is appropriate. Second, it is used by FDA to ensure that limits are placed on advertising and promotional claims and that the drug's labeling is appropriate.

FDA may request further studies when there are questions about a drug that were not sufficiently answered by the phase III studies, but which do not warrant delaying the release of what promises to be a useful new product (24). Although FDA has no explicit authority to require such studies, these "phase IV" studies are almost always performed, as the alternative would be nonapproval of the drug.

HISTORY AND OBJECTIVES OF POSTMARKETING SURVEILLANCE

As a result of 1974 hearings before the Senate Committee on Labor and Human Resources' Subcommittee on Health, the Department of Health, Education, and Welfare formed a Review Panel on New Drug Regulation. The panel issued its report in May 1977 (16).

A bill was subsequently introduced in the Senate in early 1978 to revise the drug provisions of the Food, Drug, and Cosmetic Act. A revised bill, S. 1075, the Drug Regulation Reform Act of 1979, passed the Senate in September 1979. A similar bill, H.R. 4258, was not acted on by the House of Representatives. Included in the Senate bill were the following specifications: 1) drug sponsors could be required to conduct postmarketing surveillance of a drug for up to 5 years; 2) a prescription drug could have its distribution limited if the drug could not otherwise be found to be safe and effective; 3) the standard for a drug's immediate removal from the market would be changed from the drug being an "imminent hazard to the public health" to the less stringent standard of "unreasonable risk of illness or injury to any segment of the population;" and 4) establishment of a "National Center for Drug Science."

During this period, in a speech to the Pharmaceutical Manufacturers Association, Senator Edward Kennedy (D-Mass.) suggested that a better system was needed for monitoring the use and effects of prescription drugs after they were marketed. As a result, the Joint Commission on Prescription Drug Use was established in 1976, funded largely by the drug industry, with the mandate to design a postmarketing surveillance system to detect, quantify, and describe the anticipated and unanticipated effects of marketed drugs, and to recommend a means by which information on the epidemiology of prescription drug use in the United States could be distributed regularly to interested parties. The Joint Commission issued its report in January 1980 (42), but by this time, interest in postmarketing surveillance had waned, and the commission's report and recommendations were little noticed.

In 1976, the year in which the Joint Commission was formed, an interagency agreement was signed between FDA and the Experimental Technology Incentives Program (ETIP) of the National Bureau of Standards in the Department of Commerce. The purpose of ETIP was to provide incentives or reduce barriers to technological innovation through changes in the regulatory process. ETIP's agreement with FDA was to jointly fund a program to determine if improvement in postmarketing surveillance could help reduce the regulatory requirements of the premarketing period, principally those of phase III of the IND process and those of the NDA process. The specific experiment was to develop postmarketing surveillance systems and a method of managing and evaluating the reform (11). The project concentrated on collecting the information required to design these systems (12). By 1982, FDA had assumed most of the funding, as ETIP was to be phased out that year.

A Commission on the Federal Drug Approval Process was convened in mid-1981 to examine how FDA's procedures for the approval of new drugs could be expedited without compromising

public safety and to make recommendations on the development of cost-effective postmarketing surveillance to guarantee the quick withdrawal from the market of drugs that cause significant adverse effects. The commission had its genesis in a joint hearing held in April 1981 by the House Science and Technology Committee's Subcommittee on Natural Resources, Agriculture Research, and Environment and its Subcommittee on Investigations and Oversight. The first meeting was held in July 1981. The commission completed its work and announced its general findings in the spring of 1982, and its printed report was to be released in late 1982.

FDA is examining specific ways to speed up the drug approval process. It is reviewing past phase III trials to see if longer trials or those with large samples have contributed useful information beyond that obtained in phase II and early phase III testing. Past postmarketing studies that FDA required are also being reviewed to see if they provided the information that they were designed to obtain. Data on FDA approval time are being reviewed to see what other factors may slow the approval process. And, as a pilot test, an FDA committee is reviewing the pharmacologic and clinical data on selected drugs at the end of phase II testing, and will make recommendations about the best time for gathering additional information (e.g., phase III v. the postmarketing period) (11).

In March 1982, the FDA Commissioner began a related organization by merging the Bureau of Drugs with the Bureau of Biologics, and replacing the Director of the New Drug Evaluation Division. The merged bureaus have since been designated the National Center for Drugs and Biologics.

Finally, in a related development, the Senate passed by a voice vote, in the first session of the 97th Congress, the Patent Term Restoration Act of 1981 (S. 255). The bill would restore to the term of a patent the time lost in complying with the Government's premarketing testing and review requirements, up to a maximum of 7 years. Patented products eligible for extension would not be limited to human drugs, but would include "human drugs and biologicals, antibiotic drugs, animal drugs and biologicals, food additives, color additives, pesticides, other chemical substances, medical devices, and any other product subject to Federal premarket requirements" (72). In September 1982, the House of Representatives voted on the bill under suspension of its rules. Under such conditions, a two-thirds vote was required for passage, and although the bill received a majority of the votes, it fell just short of the two-thirds majority needed.

METHODS OF SURVEILLANCE

The primary objective of postmarketing studies is to develop information about drug effects under customary conditions of drug use. Initial clues about a drug's potential effects come from the experimental studies carried out with both animals and humans in the premarketing period. Spontaneous or voluntary reporting (e.g., in letters to the editors of medical journals) is the oldest, and to date, the most productive source of new information about a drug's possible effects once a drug is marketed. Other types of studies are used to examine in more detail the possible effects of a drug. In general, these other types of studies use either cohort or case-control methods.

Thus, four types of studies are generally used to identify drug effects: 1) controlled clinical trials, 2) spontaneous or voluntary reporting, 3) cohort studies, and 4) case-control studies (23,50,61,77).

Controlled clinical trials match treatment and control groups as closely as possible, minimize bias through such methods as randomization and "double-blinding," and directly monitor patients for the duration of the study. Controlled clinical trials are considered the most definitive method for evaluating a drug's efficacy and safety, but they are often costly or impractical in specific situations, for example, when a drug's effects are

rare, or appear only after long-term use or a long latency period.

Voluntary reporting by physicians and other health providers, hospitals, and consumers may act to alert FDA and pharmaceutical firms to possible adverse effects of drugs, so that the inference of an association between a drug and an observed health condition may be further studied by cumulative, careful reporting, and confirmed or disconfirmed by more vigorous methods. Underreporting may be a serious deficiency of this method. A drug may also be erroneously associated with an adverse effect until the suspected association fails to show up in repeated, statistically validated studies.

Cohort studies follow a defined group of patients (the cohort) for a period of time. In this method, patients are not randomly assigned to groups, and there is no blinding. Cohort studies are usually prospective and observe the cohort from the beginning of drug use. A group of patients taking the drug of interest is assembled and followed to see, for example, if adverse reactions occur. A second group of patients (the controls) with the same medical condition, who are not taking the drug and who may be receiving alternative treatment, but who are otherwise matched as closely as possible with the cohort, may also be studied in parallel. The control group is used to identify the frequency of occurrence of any condition observed in the drug-exposed group which is due to causes other than the drug (i.e., the "background incidence" of the condition). In this method, patients can be directly monitored to ensure they take the drug appropriately, and to observe the drug's effects; or monitoring can be less controlled. With less control, a larger cohort can be followed, but bias is thus increased.

Case-control studies identify patients with the adverse effects to be studied (the cases), and compare them with a sample (the controls), drawn from the same cohort that gave rise to the cases. Controls are matched as closely as possible with the cases, except with regard to the drug's suspected adverse effect, to examine whether exposure to the drug is the cause. Patients with conditions suspected of being associated with a certain drug would have their medical records reviewed or be interviewed concerning the use of that drug. The histories of the controls would also be studied for information about drug use in the general population. By comparing the proportion of drug users among the cases with the proportion of drug users in the general population, it is possible to infer the relative frequency with which adverse reactions occur in users of certain drugs as compared with nonusers. A sufficient number of appropriate cases must be identified and accurate histories of exposure to drugs must be obtained.

Controlled clinical trials and prospective cohort studies can be used to determine a drug's beneficial as well as adverse effects. Case-control studies are usually used to trace adverse effects back to prior drug use. Voluntary reporting can uncover additional uses of drugs as well as their adverse effects, but reporting of adverse effects is much more common.

The ability of a particular surveillance method to detect a drug's effect depends on two factors: 1) the time that transpires between use of that drug and the occurrence of the drug's effect (the latency period), and 2) how often the effect occurs (its frequency). There are many other determining factors, such as accuracy of observation, and accuracy and completeness of medical records, but these factors present more of a problem in the design of a study's details.

Controlled clinical trials, because of their relatively short duration, will detect only acute or subacute effects. Long-term cohort studies can detect delayed effects, but the data bases necessary for such long-term, large studies are still sparse. Voluntary reporting is usually the way in which long-term effects are first identified. Long-term effects are usually confirmed through retrospective case-control studies, but such studies' reliance on historical data such as medical records can limit their accuracy.

The chance that a particular study will discover a drug effect also depends on the study's sample size and the frequency of the drug effect. For example, in a cohort study, if a drug causes blindness in 1 out of every 100 users (1/100), how many users must be observed to find one case of blind-

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ness? If there are 1 million users of the drug, there would be 10,000 users blinded. But in a small sample of only 100 users, the probability of finding one or more cases of blindness would only be 63 percent. If the sample were 200 users, the probability of finding one or more cases would increase to 86 percent. With a sample of 500, the probability would be 99 percent that at least one case of blindness would be found in the observed users.

To state it another way, what number of users would have to be observed to be 95 percent sure of finding one or more cases of blindness when they occur at a frequency of 1 in 100 users? The answer is 300 users, and the general rule is that the number of users in the sample must be three times the reciprocal of the frequency; e.g., for a frequency of 1 in 1,000, the sample would have to be 3,000 to be 95 percent sure of observing at least one case.

Except for some effects that are unique to a specific drug, many drug effects (e.g., stroke, bleeding, skin rashes) are indistinguishable from conditions due to other causes. The "background incidence" of a condition must be known before purported drug effects observed in a study can rightly be attributed to a drug.

Larger sample sizes are needed to determine a drug's effect as the background incidence of a condition increases and as the frequency of a drug's contribution to a condition decreases. For example, given a background incidence of 1/100, as the incidence of a drug's added effect decreases from 1/100 to 1/10,000, the sample size would have to increase from 1,600 to 11 million to remain 95 percent sure of observing at least one case of the added effect. The relationship between background and added incidences is also revealed in considering sample sizes at the extremes. For a known background incidence of 1/1,000 and an added incidence of 1/100, the sample size needed to observe at least one case of the added effect is only 500. But when the background incidence is 1/10 and the added incidence is only 1/10,000, the sample size must be 98 million. These illustrations merely indicate what sample size is required to observe an effect when background incidence is known.

Controlled clinical trials are used primarily for evaluating drug efficacy, not safety, because they are carried out on hundreds, or, at the most, a few thousand drug users. Their use for evaluating drugs already on the market is also limited by their high cost and logistical problems. In fact, the use of controlled clinical trials for determining efficacy alone is already constrained by these two factors (9,46).

These limitations of controlled clinical trials in evaluating the safety of marketed drugs have led to relying on cohort and case-control methods for postmarketing studies. While these latter methods can only indicate an association between a drug and observed conditions, not that the relation is causal (49,77), the cumulative experience of multiple cohort and case-control studies showing consistent associations between a drug and such an effect can lead to a high degree of confidence that the relationship is causal. The most prominent examples of drug studies showing consistent associations are those on oral contraceptives and the risks of cardiovascular disease; similar examples of nondrug studies are those on the risks of smoking.

ISSUES AND OPTIONS

Issue 1:

Revising premarketing tests and shortening the drug approval process.

The efficacy and safety tests in animals and humans specified in FDA regulations for premarketing approval are based on broad statutory language. Efforts to shorten the drug approval process have focused not on the statutory language but on the regulations issued by FDA to implement the law. Thus, the focus here is on oversight issues, not on legislative changes.

Proposals to curtail or eliminate phase III premarketing tests, or shift them to the postmarketing period, can be evaluated both theoretically and experientially.

Theoretically, phase III testing is significantly more sensitive than phase II testing. Adverse effects with an incidence of 1/100 or more are more likely than not to be detected in the 100 to 200 patients given a drug in phase II. But the theoretical sensitivity of detection rises in phase III to 1/500 with 500 patients and to 1/1,000 with 1,000 to 3,000 patients (see ch. 4, table 5).

These observations are relevant to the detection of adverse reactions, but they are not so relevant to the detection of therapeutic effects. Since a drug that helps only 1 in 100 patients would not be very effective, efficacy should be established in phase II. Phase III is intended to gather additional evidence on a drug's effectiveness for specific indications.

If phase III testing were curtailed or eliminated, there is also the question of whether premarketing evaluations would test sufficient numbers of patients to reasonably ensure a drug's safety or give substantial evidence of its efficacy. Even under current regulations, the use of a drug on human subjects is very limited before the drug is released for market: 20 to 80 patients in phase I; 100 to 200 patients in phase II; and 500 to 3,000 patients in phase III—a range of only 620 to 3,280 patients per drug (excluding controls).

In addition to theoretical criteria, **experiential criteria could be applied in considering proposals to curtail or eliminate phase III tests.** The diminished power to observe adverse drug effects that such changes theoretically entail may not in fact be found, judging on the basis of actual experience in phase III testing, or if it is, it may only concern infrequent, minor effects. Agreement of the experiential data with the differences theoretically expected would strengthen the hypothesis that curtailing phase III would lower the capacity of current premarketing tests to identify adverse reactions. If the experiential data fail to detect the theoretical differences, then a better case can be made for curtailing phase III, with or without transfer of some of its testing to the postmarketing period.

Current interpretations of the statutory requirements for "adequate tests" of safety and "substantial evidence" of efficacy emphasize methodology, as reflected in the requirement that each indication for which a drug is intended be supported by at least two well-controlled clinical trials. **But FDA can alter the criteria by which it approves drugs.** For example, propanolol, the first beta-blocking drug approved for use in the United States, was approved by an advisory committee on the basis of all the evidence presented to FDA, even though no one study was found to be adequate and well controlled (21). And in late 1981, timolol, another beta-blocker, was approved, on the basis of evidence from a foreign study, for use in preventing death and recurrent heart attacks in patients who have survived initial heart attacks (26).

The approval of propanolol and timolol illustrates that FDA can grant exceptions to its usual requirement of two well-controlled U.S.-based clinical trials. In such cases, expert judgment relies on qualitative, not quantitative, criteria in approving a drug, and such an approach falls outside the theoretical and experiential guidelines outlined above. **If FDA is to rely increasingly on such qualitative criteria through increased use of advisory committees, it will be necessary for FDA to develop general guidelines to aid the advisory committees in their deliberations.** Otherwise, in a case-by-case analysis, evidence of the same quality may lead to approval for one drug and nonapproval for another.

Issue 2:

Improving postmarketing surveillance and its role in the drug approval process.

Even if phase III testing were not curtailed or eliminated, FDA's powers in the postmarketing period could be strengthened to enhance its surveillance role.

Postmarketing surveillance "systems" that have been advocated are not systems in the formal sense, but a series of related activities oriented toward several purposes, with the regulatory approval process being only one. Three activities are most frequently mentioned. First is the building of a resource base through training of additional experts and improving epidemiologic tools such as methods for cohort and case-control studies. Second, unless a drug effect has a sufficient fre-

quency of occurrence (usually identified as 1/1,000) and for delayed effects of, for example, greater than 1 year, strengthened voluntary reporting is the most realistic method of identifying possible adverse drug reactions. Once such reactions are suspected, clinical trials, case-control, and cohort studies could be used to determine whether an association with drug use in fact exists. Third is the development of an efficient method for monitoring selected drugs after their release into the market. The most frequently mentioned mechanism is formation of prospective cohorts of drug users.

These aforementioned components of a postmarketing surveillance "system" and FDA's role in supporting and using them are oversight issues.

There are also several legislative options that could strengthen FDA's powers in the postmarketing period. The following legislative options are presented for congressional consideration.

Option 1: Give FDA the power to require postmarketing studies.

A variation of this option is for FDA to use its existing regulatory powers over advertising and promotional practices to "certify" an industry-sponsored postmarketing study.

Option 2: Give FDA the power to restrict the distribution, dispensing, and administration of a drug.

A variation of this option is for FDA to use its existing regulatory powers to develop a parallel approval process for the use of a limited group of drugs during phase III testing, such as for drugs of unusual need and promise.

Option 3: Change the standard for a drug's removal from the market from "imminent hazard to the public health" to "unreasonable risk of illness to any segment of the population" or some other less stringent standard.

2.
The Drug Approval Process

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2.
The Drug Approval Process

A drug's sponsor must provide: 1) adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use und the conditions prescribed, recommended, or suggested; and 2) substantial evidence that the drug will have the effect it purports or is represented to have. "Substantial evidence" means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have" (21 U.S.C., sec. 355(d)). (See app. A for selected sections of the act.)

This statutory language has led the Food and Drug Administration (FDA) in practice to establish a premarketing phase of drug testing that consists of two parts: 1) the investigational new drug (IND) application process, and 2) the filing of a new drug application (NDA).

NOTICE OF CLAIMED INVESTIGATION FOR A NEW DRUG

IND Application Process

A new drug is defined as any drug: 1) that is not generally recognized by experts to be safe and effective for the use described in the drug's labeling (except for certain so-called "grandfather drugs," i.e., those approved prior to the 1962 amendments); or 2) that has been shown to be safe and effective in clinical investigations, but has not been used to any material extent or for a material time.

A drug is considered to be new for any of the following reasons: 1) it is composed in whole or in part of a new substance (this includes active components and inert ones, such as a coating or carrier); 2) it is a new combination of approved drugs; 3) it is an approved combination in a new ratio; 4) it is an approved drug with a proposed new use (i.e., a use for which the drug has not been approved); or 5) it is an approved drug with a proposed new dose or new method or duration of administration (21 CFR 310.3(g)).

A sponsor is the entity responsible for the entire investigation of a new drug. The sponsor can be an individual, a partnership, a corporation, or another agency of the Government (e.g., the National Cancer Institute). In testing a new drug, a sponsor may use a number of different investigators.

A sponsor wishing to investigate a new drug by means of clinical tests in humans must first carry out various studies in animals (see table 1). Such studies examine acute and chronic drug toxicity at different dose levels, by different routes of administration, and in different species. Biochemical data are also obtained on the drug's absorption, distribution, metabolism, and excretion. The data from chronic animal studies, which can take over 2 years to collect and analyze, are not ordinarily required for permission to proceed to human trials. Long-term animal tests must also be undertaken at the same time that the drug is being tested in humans, particularly for drugs intended for use over long periods of time, as for chronic diseases and oral contraception. The purpose of long-term animal tests is to investigate the drug's toxicity (e.g., carcinogenicity) when taken chronically, and its effects on fertility, reproduction, and fetal development (e.g., teratogenicity).

The point at which FDA becomes involved in the development process for a new drug is when a sponsor desires to investigate the drug's safety and effectiveness via clinical tests in humans. Be-

Table 1.—Guidelines for Duration of Animal Toxicity Studies for Oral and Parenteral Drugs

Expected duration of continuous administration to humans	Phase of clinical investigation	Duration of subacute or chronic toxicity studies in animals
Several days	I, II, III, NDA[a]	Two species; 2 weeks
Up to 2 weeks	I	Two species; 2 weeks
	II	Two species; 2 months
	III, NDA[a]	Two species; up to 3 months
Up to 3 months	I, II	Two species; 4 weeks
	III	Two species; 3 months
	NDA[a]	Two species; up to 6 months[b]
6 months to unlimited	I, II	Two species; 3 months
	III	Two species; 6 months or longer
	NDA[a]	Two species; 12 months[b] (nonrodent) 18 months[b] (rodent)

[a]New drug application.
[b]Although as yet there has been no formal updating of these guidelines, they have been expanded to include 2-year animal toxicity and carcinogenicity studies for those drugs that would be administered chronically or intermittently in a large population (e.g., contraceptives). These studies are presently being required on a drug-by-drug basis as investigational new drugs are reviewed.

SOURCE: U.S. Food and Drug Administration.

fore proceeding, the sponsor must file an IND application with the Office of Drugs in FDA's National Center for Drugs and Biologics. The 1962 amendments to the Food, Drug, and Cosmetic Act, by empowering the Secretary of Health and Human Services to write specific requirements, effectively require that all results from testing a new drug in humans be submitted by the sponsor of the drug and approved by FDA under an IND. In filing the IND application, the sponsor agrees to refrain from beginning studies for 30 days, but may begin them after that time unless FDA asks the sponsor to continue to avoid or to restrict use of the drug in humans. The 30-day delay can be waived upon a showing of good reason.

The IND application describes the qualifications of the investigators and the planned trials, and includes a chemical description of the drug and available data on its pharmacology and toxicology as collected in animal studies and in prior human studies, if any (e.g., those conducted in foreign countries). If the necessary animal tests have been carried out and give evidence for the safety of the proposed human use, if the drug is adequately characterized so that the tests will be meaningful, and if the proposed human studies appear reasonably safe, the IND application is usually approved. The sponsor may then proceed with clinical testing if FDA does not raise objections within 30 days.

Once the IND application is approved, additional protocols and investigations can be added. FDA sets no time limit on the IND process as long as annual reports in the form of summaries are submitted and serious adverse reactions are promptly reported. All data on drug effectiveness, including that from clinical studies in patients, as well as chemical and animal data, are considered to be the sponsor's property and subject to protection as trade secrets. If, at any time during the tests on human subjects, the continuance of those tests is determined to endanger public health, they can be stopped immediately.

The clinical investigations of a new drug—i.e., studies in humans—are divided into three phases that in actual practice are not so distinctly separated (see table 2) (24).

Phase I: Clinical Pharmacology is the initial use of the drug on humans. The purpose of this phase is to determine levels of tolerance (toxicity), to begin to ascertain safe dose ranges, and, in some cases, to study drug efficacy in selected patients. The total number of healthy volunteer subjects and patients administered the drug ranges from about 20 to 80. At this stage, many drugs are screened out because their safety is found to be seriously questionable or because they are found to be inactive in humans. If the drug appears to be well tolerated, it may go on to the next stage of testing.

Table 2.—Studies Required in FDA's Premarketing Drug Approval Process

Phase I:
- — Studies in normal volunteers or relatively healthy patients to determine safety and pharmacologic effects.
- — Small studies in patients to determine clinical effectiveness.
- — Total number of subjects—up to 80 administered the investigational drug.

Phase II:
- — Controlled clinical trials to determine appropriate doses, safety, and effectiveness.
- — Total number of patients—about 200 administered the investigational drug.

Phase III:
- — Controlled and uncontrolled clinical trials to determine safety and effectiveness and to support labeling claims.
- — Total number of patients—about 500 to 3,000 administered the investigational drug.

SOURCE: U.S. Food and Drug Administration.

Phase II: Clinical Investigations are the earliest investigations specifically designed to demonstrate effectiveness and relative safety, and to include controlled studies. In this phase, the drug is administered to 100 to 200 patients, under rigid protocols and close monitoring. If the therapeutic value of the drug has been demonstrated, and it appears to have no serious adverse effects, it may then enter the final stage of testing.

Phase III: Clinical Trials are expanded controlled and uncontrolled trials. They are carried out on 500 to 3,000 patients in situations similar to those of actual clinical practice—in clinics, outpatient hospital facilities, and private practice. These studies are performed after a drug's efficacy has been established, at least to some degree, and are intended to gather additional evidence of drug effectiveness, to discover rarer drug effects or effects that develop after longer periods, and to better define the frequency and severity of more common effects as well as the proper use of the drug (e.g., by identifying best dose, dose interval, and the drug's interactions with other drugs). Adequate and well-controlled trials that give evidence of a drug's effectiveness, accompanied by complete case records for each patient, are sometimes termed **pivotal studies**. FDA usually requires at least two independent well-controlled studies to approve an NDA, the following stage of the drug approval process, though more than one drug indication can be evaluated in a single study. (These requirements are currently under review; see ch. 3.)

Compassionate or Treatment IND

FDA has recognized that under special circumstances, when a patient has exhausted all other therapies for a life-threatening disease, a drug that might be of value but is still unapproved should be made available. Investigational drugs can be made available under a "compassionate" or "treatment" IND. The drugs made available are generally in phase III of clinical testing.

Physicians can obtain an investigational drug if they have a patient with a disease that is life-threatening or significantly impairs the quality of life, and the patient is allergic or resistant to existing methods of treatment. Under such circumstances, FDA usually recommends that the physician contact the medical director of the company investigating the drug to inquire whether the company will accept the physician as an investigator under its IND application for that particular patient. The company may also supply the drug to the physician, who files his or her own IND application.

Sometimes these treatment uses can become quite extensive, especially when available therapy is unsatisfactory, for example, in the treatment of serious cardiac arrhythmia and angina pectoris. According to Robert Temple, recently appointed director of the Office of Drugs' New Drug Evaluation Division, promising new antiarrhythmics and antianginal drugs have been given to thousands of patients under these circumstances. But the compassionate IND procedure may be inadequate for providing a needed drug that is still in the process of being approved when patients are distant from a medical center or when physicians are not familiar with FDA procedures.

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THE NEW DRUG APPLICATION PROCESS

After the completion of required testing under the IND, if the sponsor believes that the drug's safety and effectiveness have been proved and that the drug has commercial potential, the sponsor may file an NDA, a request for FDA's permission to market the drug in interstate commerce. This application includes everything the sponsor considers necessary for meeting the statutory requirements: 1) full reports of animal and clinical studies carried out to determine whether the drug is safe and effective; 2) a statement of the drug's composition; 3) a description of the methods, facilities, and controls used in the drug's manufacturing, processing, and packaging; 4) samples of the drug and its components as may be required; and 5) a copy of the proposed labeling. The labeling describes what is known about the drug: the approved uses, dosages, the indications for which its effectiveness is approved, and its known adverse side effects. The final wording of the labeling is negotiated between FDA and the sponsor, and must be formally approved as part of the NDA.

All INDs are classified by chemical type and therapeutic potential so that those drugs considered by FDA to be of particular therapeutic importance can receive priority review (see table 3). The highest classification is for a drug that is both a new molecular entity (type 1) and that might represent an important therapeutic gain (type A) —a type 1A drug. The next highest classification is given to a new molecular entity that represents a modest therapeutic gain (a type 1B drug). But skepticism has been expressed by some industry representatives as to whether a correct determination of the potential benefits of a drug can be made at the time of NDA submission.

After the NDA is filed, a team of FDA reviewers analyzes the sponsor's summaries of the data or, when needed, the actual data. The review team includes a physician, who reviews the clinical test results; a pharmacologist, who reviews the animal test results; and a chemist, who reviews the chemical data and manufacturing controls and processes; supported by a biopharmaceutic specialist, a biometrician, and, when applicable, a microbiologist. The main objective of the process is to ensure that the data from the clinical experiments support the claims for the drug's safety and efficacy in the labeling the sponsor submitted.

NDAs may be presented for consideration to advisory committees composed of experts (mostly nongovernmental) in the various subspecialties of medicine, in clinical pharmacology, and in biometrics. The committees recommend whether or not an NDA should be approved to market a drug and, if the drug is approved, what wording should appear in its labeling. They also may recommend whether the sponsor should be requested to carry out additional studies after the drug is marketed. If the committees recommend against approval, they identify deficiencies and may suggest new studies that need to be done by the sponsor to further investigate the drug's safety and efficacy.

FDA invites a sponsor to confer with FDA about important new therapeutic drugs during the drugs' investigational phases. Usually, such conferences are arranged at the end of phase II, when a drug's degree of efficacy and safety has been

Table 3.—FDA's Drug Classification System

Chemical type		Therapeutic type	
Type 1	New molecular entity	Type A	Important therapeutic gain
Type 2	New salt, ester, or derivative	Type B	Modest therapeutic gain
Type 3	New formulation	Type C	Little or no therapeutic gain
Type 4	New combination	Type D	Decreased safety or efficacy compared with other drugs but has some compensating virtue
Type 5	Duplicate of an already marketed drug		
Type 6	Already marketed product by same firm—primarily used for new indications		

SOURCE: U.S. Food and Drug Administration.

largely established. The purpose of the conferences is to discuss whether the studies to date are acceptable, in view of the drug's proposed indications and the claims made for the drug, and whether the additional controlled studies proposed for phase III will be adequate for the NDA's approval.

FDA must approve or disapprove a submitted or resubmitted NDA within 180 days. It may take longer if the sponsor and FDA agree on an additional period of time. An FDA study of the review time for approved NDAs found that in 1976, it was 25.9 months, in 1977, 26.6 months, and in 1978, 33.3 months (12). In the first half of 1979, however, the average time had been reduced to 20 months (30). These approval times include several resubmissions of the NDAs either to correct deficiencies noted in them during FDA review, or because the sponsor obtained a large amount of additional data. Furthermore, the total amount of information required for an NDA has increased markedly since 1938, when the 180-day limit was imposed. In 1938, the required information consisted of data from short-term animal toxicology studies, along with that from a few studies in humans. Today, an NDA must contain the reports of numerous short- and long-term animal studies along with the reports of various clinical trials to demonstrate the drug's safety and effectiveness in humans.

Should FDA decide to refuse approval, the sponsor receives a "nonapprovable" letter explaining why the NDA fails to fulfill statutory requirements. An applicant's approval can be refused for any of the following reasons:

- Drug safety has not been studied by all reasonably applicable tests.
- The drug is not safe for the intended use.
- The drug's manufacturing processes are not adequate to ensure its identity, strength, quality, and purity.
- Substantial evidence of the drug's effectiveness is lacking; i.e., the clinical investigations were not adequate or well controlled or their results do not adequately support the claims made.
- The labeling is false or misleading in any particular.
- The application is missing data, e.g., on bioavailability or bioequivalence or on the environmental impact of the manufacturing process.

If the clinical trials establish that a drug is effective for its intended indications, FDA must decide whether the drug's benefits outweigh its risks. FDA does not require a sponsor to prove that a drug is safer than available drugs, nor more effective, nor even as effective as other treatments in order to receive permission to market the drug. In some cases, a drug may be less safe than an alternative therapy. Although most manufacturers normally would not be interested in marketing a drug whose benefit/risk ratio is less than that of a treatment already available, FDA recognizes that there are times when such drugs should be made available.

When presented with an NDA in which the data clearly show a drug to have an inferior benefit/risk ratio, FDA considers the indications for which the drug is offered. Thus, such drugs when intended to treat a life-shortening condition might receive approval, while such drugs when intended for lesser indications (e.g., mild analgesics that are less safe and no more effective than aspirin) would not. Obviously, the decisions that cause the most difficulty are those concerning drugs between these extremes (22).

Abbreviated New Drug Application

FDA has established an abbreviated new drug application (ANDA) for generic versions of drugs first marketed between 1938 and 1962. These drugs require less testing for approval than do original versions of a drug. The amount of information required for approval of such generic drugs varies, depending on the nature of the drug. The ANDA policy does not apply to drugs marketed after 1962. Approval of generic copies of these recent drugs requires a standard NDA, but FDA has been willing to accept published reports demonstrating the safety and efficacy of these drugs. NDAs that rely on published reports are sometimes referred to as "paper" NDAs.

REQUIREMENTS FOLLOWING APPROVAL

Once the NDA has been approved, the sponsor is required to keep records and submit reports about the drug. This information is used to: 1) maintain the procedures and safeguards for manufacturing established during the approval process, 2) ensure that there are limits placed on advertising and promotional claims and that the drug's labeling is appropriate, and 3) provide the basis for FDA's removal of a drug from the market, when such action is appropriate.

The studies carried out before a drug is released have a number of inherent limitations with respect to the amount and kind of information they generate, limitations that include the following:

- The patients in premarketing studies (even in phase III) do not represent all those who would ultimately take the drug. Thus, a drug's effects on special patient populations not specifically studied in premarketing tests may not be known. Such special populations include patients who are taking several medications concurrently, those having diseases in addition to the one treated by the drug, and those who suffer more severely from the disease being treated than the patients in the study groups. Similarly, when phase III studies are conducted on children (e.g., when they are to be a drug's chief recipients), usually only very small groups of patients are studied, and the entire age range of concern (e.g., including newborns) is not studied for ethical and other reasons.
- The total number of people exposed to the drug in premarketing studies is relatively small; therefore, uncommon adverse reactions (i.e., those less frequent than 1/1,000) are unlikely to be detected.
- The duration of exposure to the drug in premarketing studies is relatively brief (12 to 24 months at most); therefore, adverse effects that only appear after long-term use or that require a latent interval after exposure to develop (e.g., cancer) cannot be detected.
- Clinical trials must be conducted according to strict protocols (regarding dosages, duration of treatment, etc.), and they are usually carried out by specialists in large medical centers where such research can be done. Thus, the effects a drug might have when administered by a regular physician in an office or outpatient clinic, when patient compliance to a treatment regimen is less controlled, cannot be fully assessed.
- In premarketing studies, a drug is often evaluated for only one purpose (e.g., treatment of hypertension), but it may have another use (e.g., treatment of angina pectoris). (In its labeling, the only drug indications that may appear are those that have been explicitly tested and approved).

FDA has several mechanisms to obtain information about drugs once they have been approved for marketing.

FDA may request further studies when questions about a drug remain unanswered by phase III studies but do not warrant delaying the release of what may be a useful new product. These studies are referred to as "phase IV" studies. Although this designation is not defined in FDA regulations, it is discussed in the guidelines (24). The studies' nature depends on the question to be resolved, and their design is negotiated between the drug's manufacturer and FDA through its New Drug Evaluation Division in the Office of Drugs.

Phase IV postmarketing studies can be of several types (24):

- Additional studies to elucidate the incidence of adverse reactions, to explore a specific pharmacologic effect, or to obtain information of a circumscribed nature.
- Large-scale, long-term studies to determine the effect of a drug on morbidity and mortality.
- Additional clinical trials similar to those in phase III, to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data which would ordinarily be obtained before marketing.
- Clinical trials in a patient population not adequately studied in the premarketing phase; e.g., children.

- Clinical trials for an indication for which it is presumed that the drug, once available, will be used.

In general, phase IV studies have been requested when a drug is likely to be widely used, and important safety and efficacy questions about it remain. Phase IV studies may be requested, for example: 1) when there are suspected or known adverse drug reactions (ADRs) associated with the drug, in order to confirm the ADRs and to determine their true incidence; 2) when a drug belongs to a class of drugs known to be associated with a serious ADR, but its incidence may not be high enough to observe in the limited number of patients in phase III studies; 3) when the drug is one that will be used with children, and it was not tested on them in the premarketing studies; 4) if the drug is likely to be used therapeutically in combination with another drug, and there is reason to be concerned about the toxicity of the combination; and 5) if a drug approved for one indication is very likely to be used for several other indications. (Studies may be required for each of the other uses. For example, most beta-adrenergic blocking agents, such as propanolol, are used in the treatment of angina, hypertension, and arrhythmia, but an NDA may be approved when the use of a drug for only one of these indications has been documented. Even though the drug has only one approved use, it will likely be prescribed for the other two uses.)

Phase IV studies may be typical clinical trials similar to those carried out in the premarketing period. They may also use other surveillance methods. (See ch. 4 and its case studies of streptokinase and cimetidine.)

Finally, FDA receives information on marketed drugs through various kinds of monitoring of adverse drug reactions carried out by the Division of Drug Experience in the Office of Drugs:

- the Spontaneous Reaction Reporting Program, in which ADRs are reported to FDA by physicians, pharmacists, hospitals, and manufacturers (the last kind of reporting is mandatory);
- a monthly review of the medical literature on ADRs (reports to medical journals, letters to the editor, etc.);
- intensive surveillance and epidemiological studies of ADRs in selected hospitalized and ambulatory populations;
- several specialized registries that collect and analyze possible ADRs; and
- the World Health Organization (WHO), which sends reports to FDA summarizing the ADRs added to its system in the previous year. FDA reciprocates by providing U.S. data to WHO.

This report focuses on the regulatory uses of such postmarketing surveillance. Past studies of this issue have also focused on the need for systematic evaluations in the postmarketing period regardless of their importance for regulation, for example, in order to build a resource base of scientists, evaluation methods, and data sources for the better understanding and use of drugs once they are marketed. The evolutionary context of postmarketing surveillance is summarized in chapter 3.

3.
History and Objectives of Postmarketing Surveillance

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3. History and Objectives of Postmarketing Surveillance

In the 1960's, at least two serious drug reactions were observed in many patients. The drug thalidomide, taken worldwide, led to limb deformities (phocomelia) in the newborns of those mothers who took the drug while pregnant. Less known, and almost exclusively observed in Japan, was the optic nerve damage (subacute myelo-optic-neuropathy) and other adverse effects from the drug clioquinol, over which almost 4,000 civil suits were still pending in 1979 (68). And in Great Britain in the early 1970's, more than 4 years after the drug had been introduced there, the "practolol syndrome" was uncovered. Practolol, a drug used to treat cardiovascular disease, was eventually found to cause skin rashes, eye lesions, hearing impairment, and sclerosing peritonitis (56), with deaths occurring in about 2 percent of reported cases (37).

Great Britain, with its national health system, already had a voluntary reporting system (37). The national health system had instituted the use of "yellow cards" for reporting suspected adverse drug reactions (see fig. 1). As a guide to reporting, certain drugs are marked the first 4 years after they are marketed with an inverted black triangle in a booklet, the *Monthly Index of Medical Specialties,* which is distributed to physicians and used as a source of information for prescribing drugs more frequently than any other publication. In 1976, a slip of yellow paper was inserted into prescription pads to remind physicians to report reactions, leading to a large and consistent increase in the rate of reporting. Many British drug companies now use the yellow card, and the yellow card system and reports from drug companies together yield 90 percent of all reports of suspected adverse drug reactions (ADRs) (see table 4).

The delayed discovery of practolol's adverse effects spurred efforts to improve postmarketing surveillance, and several international meetings quickly followed in Sestri Levante, Italy (20), Honolulu, Hawaii (33), and London (53). In Great Britain, efforts focused on "early detection of adverse drug reactions by recording all adverse events occurring in a specified number of patients for an appropriate period of time; endeavoring to avoid collecting masses of unusable data and minimizing costs" (75). Thus, the early impetus was toward monitoring new drugs for adverse effects through some type of program that would help fill the gap between identifying those adverse effects sufficiently common to be detected in the premarketing trials, and identifying those so rare that voluntary reporting after marketing is their most feasible form of monitoring. The proposed methods all centered around the prescribing practices of physicians, with the experience of their patients on new drugs being examined periodically through questionnaires to the prescribing physicians. Such methods of monitoring include registered release (17), recorded release (36), and monitored release (45,79).

More recently, the objectives of postmarketing surveillance in Great Britain have been expanded, though not implemented (35):

> The need for PMS [postmarketing surveillance] is not restricted to new drugs. Some of those already marketed for many years may increase the risk of chronic disease or may have long-delayed carcinogenic effects, as illustrated in the United States by the cases of vaginal adenocarcinoma in the adolescent female children of women who took diethylstilbestrol during pregnancy.
>
> PMS should also include assessment of efficacy, especially of long-term treatment. Very little is known of the *relative* merits of members of groups of drugs such as hypotensive or anti-diabetic agents, anti-rheumatics or psychotropics. Prescribers need to know the most effective treatment available just as much as they need to know the risks involved, but government drug regulatory authorities (DRAs) are reluctant to become involved in relative efficacy, and drug companies are not naturally inclined to invest in comparisons of closely related compounds which may not show their own product to be the best.

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Figure 1.—Yellow Card Report Form Used in Great Britain

IN CONFIDENCE—REPORT ON SUSPECTED ADVERSE DRUG REACTIONS

1. Please report all reactions to recently introduced drugs and serious or unusual reactions to other drugs. (Vaccines should be regarded as drugs).
2. Record on the top line the drug you suspect of causing the adverse reaction.
3. Record all other drugs, including self-medication, takenin the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Do not be deterred from reporting because some details are not known.

NAME OF PATIENT
(To allow linkage with other reports for same patient. Also give record number for hospital patient)

SEX

AGE OR DATE OF BIRTH

WEIGHT

DRUGS* (Give brand name if known)	ROUTE	DAILY DOSE	DATE STARTED	DATE ENDED	INDICATIONS

*For Vaccines give Batch No.

REACTIONS	STARTED	ENDED	OUTCOME (e.g. fatal, recovered)

ADDITIONAL NOTES

REPORTING DOCTOR

Name

Address

Tel. No.

Signature

Date

Figure 1.—Yellow Card—Continued

REPORTING ADVERSE REACTIONS: GUIDELINES

DO NOT REPORT
1. Deliberate or accidental overdose
2. Overdose due to errors of prescribing or adminstration
3. Excessive but otherwise 'normal' effects of drugs whose dose has to be carefully titrated (e.g., insulin, hypotensives, anticoagulants)
4. Familiar relative overdose—excessive effect of a normal dose due to known predisposing factors (e.g., digoxin toxicity in presence of hypokalaemia; toxicity in patients with impaired renal function)
5. Inevitable side effects produced by known pharmacological activities of a drug (e.g., dry mouth with anticholinergic drugs, tricyclic antidepressants, etc.; and hyperuricaemia with diuretics)

REPORT ALL
1. Drug interactions—known or suspected
2. Reactions to new drugs marketed for less than 3 years
3. Totally unexpected or unexplained events (including death) which could be drug induced
4. Congenital abnormalities
5. Infrequent reactions causing significant morbidity even if well known

CHECK LIST FOR REPORTING (not comprehensive)

General	a. anaphylaxis b. all serious skin rashes c. all blood dyscrasias d. thrombosis associated with oestrogens or oral contraceptives
Gastro-Intestinal	a. jaundice b. malabsorption c. intestinal ulceration d. severe bleeding
Cardovascular	a. myocardial toxicity, e.g., unexpected arrhythmias (exclude digoxin) b. hypertensive reactions
Respiratory	a. brohchospasm b. non-infective lung disease, e.g., pneumonitis, fibrosis
Nervous System	a. convulsions b. unexpected confusional states (hallucination or psychotic reactions) c. unexpected extrapyramidal effects (exclude phenothiazines and butyrophenones) d. peripheral neuropathy e. neuromuscular blockade f. myopathy and myalgia
Eye & Ear	all reactions
Endocrines	a. unexpected reactions b. amenorrhoea c. infertility **Exclude** gynaecomastia, fluid retention, hypokalaemiaemia, hyperkalaemia, hypoglycaemia, hyperglycaemia, hyperuricaema porphyria (if produced by drugs known to have these effects)
Renal	all nephrotoxicity **Exclude** urinary retention induced by diuretics or due to anticholinergic drugs
Joints	a. all arthropathies b. D.L.E. syndrome

SOURCE: Committee on Safety of Medicines, London.

Table 4.—Percentage of Reports of Suspected ADRs in Great Britain by Class of Reporter and Method Used[a]

	Percentage of reports by class of reporter				
Method used	General practitioner	Hospital consultant	Hospital junior	Others (e.g., coroner)	All reporters
Yellow card	58.3%	6.3%	9.7%	1.7%	76.0%
Drug company	6.2	4.5	2.9	—	13.6
Correspondence	1.7	0.8	0.4	4.6	7.5
Death certificates	0.2	—	1.3	0.9	2.4
Medical journal	—	0.2	0.3	—	0.5
All methods	66.4%	11.8%	14.6%	7.2%	100.0%

[a]Based on random 10 percent sample of approximately 12,000 recent reports up to June 1978.

SOURCE: W. H. W. Inman (ed.), "The United Kingdom," in *Monitoring for Drug Safety* (Philadelphia: J. B. Lippincott Co., 1980).

Furthermore, an earlier suggestion linked postmarketing surveillance with restricted release of drugs (75):

> A case could be made for an immediate or restricted release system for the introduction of new drugs before their widespread use, half way between clinical trials and the monitored release proposals. Because of inevitable delays, it is possible that by the time 5,000-10,000 cases have been fully monitored by any of the above schemes, many more patients will have been exposed to the drug so that any serious adverse reactions in the monitored group are duplicated in those patients not fully monitored. The duration of the "restricted release" phase would depend on the drug and disease concerned. Monitoring of patients would continue, when appropriate, after the drug became generally available.

In the United States, the Food and Drug Administration's (FDA's) drug approval process was already under intense scrutiny in the early 1970's. As a result of 1974 hearings before the Subcommittee on Health, Senate Committee on Labor and Human Resources, chaired by Senator Edward Kennedy (D-Mass.), the Department of Health, Education, and Welfare formed a Review Panel on New Drug Regulation. This panel, which convened in February 1975 and issued its report in May 1977 (16), addressed two issues: 1) whether the drug law requirements for premarketing testing unnecessarily delayed the availability of valuable prescription drugs, and 2) whether the drug industry exerted undue influence on FDA decisions. The panel concluded that there was insufficient evidence on the first question and no widespread improper influence. It also identified four categories of deficiencies in the regulation of drugs: 1) openness and public accountability, 2) FDA's science environment, 3) standards and procedures for premarketing approval, and 4) FDA's role in the postmarketing period (16,18).

Senators Kennedy, Javits, and others then introduced a bill in early 1978 to revise the drug provisions of the Food, Drug, and Cosmetic Act. A revised bill, S. 1075, the Drug Regulation Reform Act of 1979, passed the Senate in September 1979. However, a similar bill, H.R. 4258, was not acted on by the House of Representatives. Included in the Senate bill were these proposed changes in existing law: 1) drug sponsors could be required to conduct postmarketing surveillance of a drug for up to 5 years; 2) a prescription drug could have its distribution limited if it could not otherwise be found to be safe and effective; 3) the standard for a drug's immediate removal from the market would be changed from the drug being an "imminent hazard to the public health" to the less stringent standard of "unreasonable risk of illness or injury to any segment of the population;" and 4) establishment of a "National Center for Drug Science."

During this period, in a speech to the Pharmaceutical Manufacturers Association, Senator Kennedy suggested that a better system was needed for monitoring the use and effects of prescription drugs after they were marketed. As a result, the Joint Commission on Prescription Drug Use was established in 1976, funded largely by the drug industry, with the mandate to design a postmarketing surveillance system to detect, quantify, and describe the anticipated and unanticipated effects of marketed drugs, and to recommend a means by which information on the epidemiology of prescription drug use in the United States could be distributed regularly to interested parties. The Joint Commission issued its report in January 1980 with the following five conclusions and recommendations identified as its most important ones (see app. B for the complete list) (42):

1. A systematic and comprehensive system of postmarketing drug surveillance should be developed in the United States.
2. Such a system should be able to detect important adverse drug reactions that occur more frequently than once per thousand uses of a drug, to develop methods to detect less frequent reactions and to evaluate the beneficial effects of drugs as used in ordinary practice. New methods will have to be developed for the study of delayed drug effects, including both therapeutic and adverse effects.
3. An integral function of the postmarketing surveillance system should be to report the uses and effects of new and old prescription drugs.
4. Recognizing the progress that FDA has made in the area of postmarketing drug surveillance in the last 3 years, the Commission recommends that PMS [postmarketing surveillance] should be a priority program of the FDA and that the FDA should continue to strengthen its program in this area.

5. A private, nonprofit Center for Drug Surveillance (CDS) should be established to further the development of a postmarketing surveillance system in the United States. This center should foster cooperation among existing postmarketing surveillance programs, develop new methods for carrying out surveillance, train scientists in the disciplines needed for doing postmarketing surveillance, and educate both providers and recipients of prescription drugs about the effects of these drugs.

In 1976, the year in which the Joint Commission was formed, an interagency agreement was signed between FDA and the Experimental Technology Incentives Program (ETIP) at the National Bureau of Standards of the Department of Commerce. The purpose of ETIP was to provide incentives or reduce barriers to technological innovation through changes in the regulatory process. ETIP's agreement with FDA was to jointly fund a program to determine if improvement in postmarketing surveillance could help reduce the regulatory requirements of the premarketing period, principally those of phase III of the investigational new drug process and those of the following new drug application process. The specific experiment was to develop postmarketing surveillance systems and a method of managing and evaluating the reform (11).

The project concentrated on collecting data to design such systems, and issued a status report in 1981 (12). Another report will be issued by the project in 1982. FDA has assumed most of the funding, and the Department of Commerce was to phase out ETIP in 1982. FDA is continuing the activities originated or stimulated by the program (see ch. 5).

A Commission on the Federal Drug Approval Process was convened in mid-1981 to examine how FDA's procedures for the approval of new drugs can be expedited without compromising public safety; it is to also make recommendations on the development of cost-effective postmarketing surveillance to guarantee the quick withdrawal from the market of drugs that cause significant adverse effects. The commission had its genesis in a joint hearing held in April 1981 by the House Science and Technology Committee's Subcommittee on Natural Resources, Agriculture Research, and Environment and its Subcommittee on Investigations and Oversight. The commission's first meeting was held in July 1981, and its report was to be released in late 1982.

FDA is also examining specific ways to speed up the drug approval process. It is reviewing past phase III trials to see if longer trials or those with large sample sizes have contributed useful information beyond that obtained in phase II and early phase III testing. Past postmarketing studies that FDA has required are also being reviewed to see if they provided the information that was originally sought. FDA data on approval time, validated by interviews with FDA and the manufacturers, are being reviewed for factors that may slow the approval process. And, as a pilot test, an FDA committee is reviewing the pharmacologic and clinical data on selected drugs at the end of phase II testing, and will make recommendations about the best time to gather additional safety information (e.g., phase III v. the postmarketing period) (11). FDA Commissioner Hayes has been quoted as saying that one possible methodological change is to accept foreign data in the premarket approval process (67). These activities have resulted in proposed new rules for new drug regulation (47 *Federal Register,* pp. 46622-66, Oct. 19, 1982). In March 1982, the FDA Commissioner began a related reorganization by merging the Bureau of Drugs with the Bureau of Biologics, and replacing the Director of the New Drug Evaluation Division. The merged bureaus have since been designated the National Center for Drugs and Biologics.

Finally, in a related development, the Senate passed by a voice vote, in the first session of the 97th Congress, the Patent Term Restoration Act of 1981 (S. 255). The bill would restore to the term of a patent the time lost in complying with the Government's premarket testing and review requirements, up to a maximum of 7 years. Patented products eligible for extension would not be limited to human drugs, but would include "human drugs and biologicals, antibiotic drugs, animal drugs and biologicals, food additives, color additives, pesticides, other chemical substances, medical devices, and any other product subject to Federal premarket requirements"

(72). In September 1982, the House of Representatives voted on the bill under suspension of its rules. Under such conditions, a two-thirds vote was required for passage, and although the bill received a majority of the votes, it fell just short of the two-thirds majority needed.

Thus, in the United States, the issue of postmarketing surveillance has involved more than identifying the serious adverse effects of newly introduced drugs. It has also led to the recommendation to monitor all drugs for their effectiveness and appropriate use by patients and physicians. In addition, improvements in postmarketing surveillance have been linked to changes in the drug regulatory process. Proponents of more rapid drug approval claim that phase III testing (e.g., the chronic trials) adds little to the data collected in phase II, and that, as a consequence, phase III testing could be curtailed or shifted to the postmarketing period. On the other hand, those concerned about drug deficiencies discovered after drug approval point out that FDA has limited options once a drug has been released. Since FDA lacks authority to limit drug distribution or use, it can only try to remove a drug from the market, if such action appears appropriate.

4.
Methods of Drug Evaluation

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4. Methods of Drug Evaluation

TYPES OF STUDIES

The primary objective of postmarketing studies is to develop information about drug effects under customary conditions of drug use.

The initial clues about a drug's potential effects come from the experimental studies carried out with both animals and humans in the premarketing period. Spontaneous or voluntary reporting (e.g., in letters to the editors of medical journals) is the oldest, and to date, the most productive source of new information about a drug's possible effects once a drug is marketed. Other types of studies are used to examine in more detail the possible effects of a drug. In general, these other types of studies use either cohort or case-control methods. Thus, four types of studies are generally used to identify drug effects: 1) controlled clinical trials, 2) spontaneous or voluntary reporting, 3) cohort studies, and 4) case-control studies (23, 50,61,77).

Controlled clinical trials match treatment and control groups as closely as possible, minimize bias through such methods as randomization and "double-blinding," and directly monitor patients for the duration of the study. For example, patients can be randomly assigned to either the control or treatment group. The control group receives a placebo or an active comparison drug that looks exactly like the drug being tested, and both the investigators and patients do not know who is receiving the real drug. (Personnel not directly involved in the tests would of course know what substance each patient was receiving). In this method, possible drug effects, both therapeutic and adverse, are closely monitored, so that they are discovered as they occur.

The controlled clinical trial is considered the most definitive method for evaluating a drug's efficacy and safety, but the use of rigorous criteria for patient selection usually means that the patients tested represent only a special class of the anticipated users of the drug(s), and the carefully controlled conditions allow for study of fewer patients than in the other methods. Thus, for example, to observe drug effects that are rare or that appear only after long-term use, controlled clinical trials might be impractical or too expensive.

Voluntary reporting may be spontaneous, such as in a "letter to the editor" of a medical journal about an unusual condition observed in a patient on a particular drug, or it may be more organized, as with the "yellow card" system in Great Britain. Most of the reporting to the Food and Drug Administration (FDA) is by pharmaceutical manufacturers, who are required by law to report adverse reactions. In practice, most of the information obtained by the manufacturers originates from physicians and other health professionals. Such observations serve as warnings of possible adverse drug effects, so that the inference of an association between a drug and an observed health condition may be further studied by cumulative, careful reporting, and confirmed or disconfirmed by more vigorous methods. Underreporting is a serious deficiency of this voluntary method, and a drug may also be wrongly associated with an adverse effect until the suspected association fails to show up in repeated, statistically validated studies.

Cohort studies follow a defined group of patients (the cohort) for a period of time. In this method, patients are not randomly assigned to groups, and there is no blinding. Cohort studies are usually prospective, and observe the cohort from the beginning of drug use. A group of patients taking the drug of interest is assembled and followed to see, for example, if any adverse reactions occur. A second group of patients (the controls) with the same medical condition, who are not taking the drug and who may be receiving alternative treatment, but who are otherwise matched as closely as possible with the cohort, may be studied in parallel. The control group is used to identify the frequency of occurrence of

any condition observed in the drug-exposed group, but which must be due to causes other than the drug (the "background incidence" of the condition). In this method, patients can be directly monitored to ensure they take the drug appropriately and to observe the drug's effects; or monitoring can be less systematic. With less monitoring, a larger cohort can be followed, but bias is thus increased.

Although uncommon, a retrospective cohort study may also be conducted when purported drug-induced effects have already been observed at the time the study is started. A retrospective cohort study must accurately ascertain patients' past drug use. In principle, this could be done by a "closed" pharmacy record system, in which users have been restricted to a single supplier or payment source. In practice, the use data on individuals needs to be connected to data on their outcome, as through computer files. Medicaid, Medicare, the military, and some prepaid health maintenance organizations could be employed for this purpose (76).

Case-control studies identify patients with the adverse effects to be studied (the cases), and compare them with a sample (the controls), drawn from the same cohort that gave rise to the cases. Controls are matched as closely as possible with the cases, except with regard to the drug's suspected adverse effect, to examine whether exposure to the drug is the cause. Patients with conditions suspected of being associated with a certain drug would have their medical records reviewed or be interviewed concerning the use of that drug. The histories of the controls would also be studied for information about drug use in the general population. By comparing the proportion of drug users among the cases with the proportion of drug users in the general population, it is possible to infer the relative frequency with which adverse reactions occur in users of certain drugs as compared with nonusers. A sufficient number of appropriate cases must be identified and accurate histories of exposure to drugs must be obtained.

Among the advantages of retrospective case-control studies compared with prospective cohort studies are the smaller number of patients required in retrospective case-control studies, the relative ease of carrying out the study, the lower cost, and the shorter time needed. A disadvantage of the retrospective case-control method is that a condition must have been already identified and suspected as the effect of drug use. It is also harder to reduce bias in a retrospective study than to do so in a prospective one (65).

Bias is equally possible in cohort and case-control studies, though each kind of study is liable to a different kind of bias. For example, bias in the observations can arise with respect to identifying the effects of the drug in cohort studies and with respect to identifying the exposure in case-control studies.

Controlled clinical trials and prospective cohort studies can be used to determine a drug's beneficial as well as adverse effects. Case-control studies are usually used to trace adverse effects back to prior drug use. Voluntary reporting can uncover additional uses of drugs as well as their adverse effects, but reporting of adverse effects is much more common.

DETECTION AND ASSOCIATION

The ability of a particular surveillance method to detect a drug's effect depends on two factors: 1) the time that transpires between use of that drug and the occurrence of the drug's effect (the latency period), and 2) how often the effect occurs (its frequency). There are many other determining factors, such as accuracy of observation, and accuracy and completeness of medical records, but these factors are more a problem in the design of a study's details.

The latency of some drug effects presents a serious problem for their study. Some effects occur immediately, or within days or weeks after drug use, or with continued use of a drug. But other effects may occur long after a drug has been dis-

continued, or only when another drug is taken simultaneously, or only in patients with certain predisposing conditions. Other effects may not be manifest in the patients themselves, but rather in their children. The use of DES (diethylstilbestrol), in pregnant women, for example, has been associated with vaginal cancer in their daughters, but only after the daughters have reached adolescence.

Controlled clinical trials, because of their relatively short duration, will detect only acute or subacute effects. Long-term cohort studies can detect delayed effects, but the data bases necessary for such long-term, large studies are still sparse. Voluntary reporting is usually the way in which long-term effects are first identified. Long-term effects are usually confirmed through retrospective case-control studies, but their reliance on historical data such as medical records can limit the accuracy of these studies.

The chance that a particular study will discover a drug effect also depends on the study's sample size and the frequency of the drug effect. For example, in a cohort study, if a drug causes blindness in 1 out of every 100 users (1/100), how many users must be observed to find one case of blindness? If there were 1 million users of the drug, there would be 10,000 users blinded. But in a small sample of only 100 users, the probability of finding one or more cases of blindness in the sample would only be 63 percent. If the sample were 200 users, the probability would increase to 86 percent. With a sample of 500, the probability would be 99 percent that at least one case of blindness would be found in the observed users.

To state it another way, what number of users would have to be observed to be 95 percent sure of finding one or more cases of blindness when they occur at a frequency of 1 in 100 users? The answer is 300 users, and the general rule is that the number of users in the sample must be three times the reciprocal of the frequency; e.g., for a frequency of 1 in 1,000, the sample would have to be 3,000 to be 95 percent sure of observing at least one case. Table 5 summarizes: 1) the probabilities of observing an adverse drug reaction (ADR) for different sample sizes and frequencies, and 2) the sample size required for various frequencies of an adverse reaction to be 95 percent sure of observing that reaction. The numbers in the bottom row are the sample sizes needed to be 95 percent sure of observing at least one ADR. In table 6 are shown the sample sizes needed to be 95 percent sure of observing one, two, or three adverse reactions for the frequencies shown.

In a sample of 3,000, effects occurring at any rate higher than 1/1,000 (e.g., 1/10, 1/50, 1/200, etc.) should be observed, and there will be a 95 percent probability of observing at least one effect that occurs at a frequency of 1/1,000. How-

Table 5.—Likelihood of Observing an ADR (95% likelihood)

	Threshold for an ADR					
	1/100	1/500[a]	1/1,000[b]	1/5,000[c]	1/10,000[d]	1/50,000[e]
Number of patients in ADR study:						
100	0.63	0.18	0.10	0.02	0.01	0.002
200	0.66	0.33	0.18	0.04	0.02	0.004
500	0.99	0.63	0.39	0.10	0.05	0.01
1,000	0.99	0.86	0.63	0.18	0.10	0.02
2,000	0.99	0.98	0.86	0.33	0.18	0.04
5,000	0.99	0.99	0.99	0.63	0.39	0.10
10,000	0.99	0.99	0.99	0.86	0.63	0.18
Number of patients required to be 95% likely to observe an ADR	300	1,500	3,000	15,000	30,000	150,000

[a]For example, lymphoma from azothioprine.
[b]For example, eye damage from practolol.
[c]For example, heart attack in older women from oral contraceptives.
[d]For example, anaphylaxis from penicillan.
[e]For example, aplastic anemia from chloramphenicol.

SOURCE: D. L. Sackett, et al., "Compliance," in *Monitoring for Drug Safety*, W. H. W. Inman (ed.) (Philadelphia: J. B. Lippincott Co., 1980).

Table 6.—Number of Patients Required To Detect One, Two, or Three ADRs With No Background Incidence of Adverse Reaction (95% likelihood)

Expected incidence of adverse reaction	Required number of adverse reactions		
	1 ADR	2 ADRs	3 ADRs
1 in 100	300	480	650
1 in 200	600	960	1,300
1 in 1,000	3,000	4,800	6,500
1 in 2,000	6,000	9,600	13,000
1 in 10,000	30,000	48,000	65,000

SOURCE: J. A. Lewis, "Post-Marketing Surveillance: How Many," *Trends in Pharmacological Sciences* 2:93, 1981.

ever, except for some effects that are unique to a drug, many drug effects (e.g., stroke, heart attack) are indistinguishable from conditions due to other causes. This "background incidence" of a condition must be known before purported drug effects observed in a study can rightly be attributed to a drug.

The sample size needed to be reasonably sure that an observed condition is the drug's effect depends on the following factors: 1) the background incidence of the condition, 2) the additional incidence due to the drug, and 3) the size of the control group, if the background incidence is unknown (47). The quantitative relationships among those factors are summarized in table 7, which presents the sample sizes required to be 95 percent sure that an observed condition is due to the drug and not to some other cause.

Larger sample sizes are needed to determine a drug's effect as the background incidence of a condition increases and as the frequency of the drug's added contribution to a condition decreases. This is best explained graphically, as in figure 2. In this example, the background incidence in every case is 1/100. As the incidence of the added effect decreases from 1 in 100 to 1 in 10,000, the sample size has to increase from 1,600 to 11 million to remain 95 percent sure of observing the added effect (see the rows in table 7 representing a known background incidence of 1 in 100).

The relationship between background and added incidences is also revealed in considering sample sizes at the extremes. For a known background incidence of 1 in 1,000 and an added incidence of 1 in 100, the sample size needed to observe at least one case of the added effect is only 500. But when the background incidence is 1 in 10 and the added incidence is only 1 in 10,000, the sample size must be 98 million (table 7).

Table 7 also illustrates that another factor could increase the sample size that a study requires. If the background incidence is not known and has to be estimated through observation of control groups, the smaller the size of the control group, the larger the sample size of drug users must be for the same degree of confidence in the results (compare the sample sizes required for control groups equal to the treated group and for those five times its size).

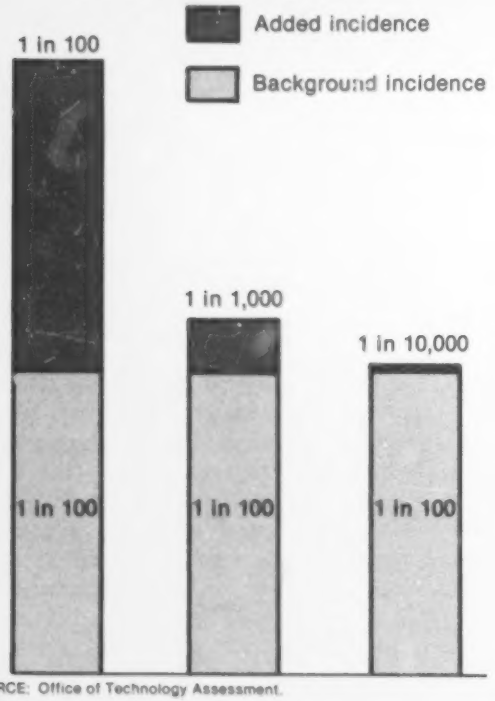
If there is a background incidence, the sample size needed to observe a drug-induced effect rises dramatically. Recall that a sample size of 3,000 was needed to be 95 percent sure of observing at least one drug-induced effect with a frequency of

Table 7.—Number of Patients Required in Drug-Treated Group To Detect One ADR With Background Incidence of Adverse Reaction (95% likelihood)

Size of control group	Background incidence of adverse reaction	Number of patients required with additional incidence of adverse reaction to drug		
		1 in 100	1 in 1,000	1 in 10,000
"Infinite" (background incidence known)	1 in 10	10,000	980,000	98,000,000
	1 in 100	1,600	110,000	11,000,000
	1 in 1,000	500	16,000	1,100,000
Five times as big as treated group	1 in 10	12,000	1,200,000	120,000,000
	1 in 100	1,900	130,000	13,000,000
	1 in 1,000	700	19,000	1,400,000
Equal to treated group	1 in 10	20,000	2,000,000	200,000,000
	1 in 100	3,200	220,000	22,000,000
	1 in 1,000	1,300	32,000	2,300,000

SOURCE: J. A. Lewis, "Post-Marketing Surveillance: How Many," *Trends in Pharmacological Sciences* 2:93, 1981.

Figure 2.—Comparison of Additional Drug-Induced Effects of Decreasing Incidences



SOURCE: Office of Technology Assessment.

1 in 1,000 and with no background incidence (table 6). If the background incidence is also 1 in 1,000, the sample size required rises to 16,000. A background incidence higher than the drug's added incidence increases the sample size required even more dramatically (to 110,000 and 980,000 for background incidences of 1 in 100 and 1 in 10 in table 7).

Many studies monitor for several effects, not just one, and some apparent drug effects may have occurred by chance. Minimizing these chance relationships also increases the sample size required. Table 8 illustrates the hypothetical case where 100 effects will be examined in one study, and the sample size reflects a 95 percent chance that the observed effects will be related to use of the drug.

These sample size illustrations reflect, at the 95 percent confidence level, that an effect will be observed and whether that effect can be attributed to drug use. They do not provide a good estimate of the added incidence of the effect from the drug (recall from table 6 that a sample size of 3,000 is needed just to detect at least one effect that has an incidence of 1 in 1,000).

Controlled clinical trials are used primarily for evaluating drug efficacy, not safety, because they are carried out on hundreds, or, at the most, a few thousand drug users. Their use for evaluating drugs already on the market is also limited by their high cost and logistical problems. In fact, the use of controlled clinical trials for determining efficacy alone is already constrained by these two factors (9,46).

Table 8.—Number of Patients Required in Drug-Treated Group To Allow for Examination of 100 Adverse Reactions (95% likelihood)

Size of control group	Background incidence of adverse reaction	Number of patients required with additional incidence of adverse reaction to drug		
		1 in 100	1 in 1,000	1 in 10,000
"Infinite" (background incidence known)	1 in 10	23,000	2,200,000	220,000,000
	1 in 100	3,100	250,000	24,000,000
	1 in 1,000	800	32,000	2,500,000
Five times as big as treated group	1 in 10	27,000	2,600,000	260,000,000
	1 in 100	4,000	300,000	29,000,000
	1 in 1,000	1,300	40,000	3,000,000
Equal to treated group	1 in 10	46,000	4,400,000	440,000,000
	1 in 100	7,200	510,000	48,000,000
	1 in 1,000	2,900	73,000	5,100,000

SOURCE: J. A. Lewis, "Post-Marketing Surveillance: How Many," *Trends in Pharmacological Sciences* 2:93, 1981.

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These limitations of controlled clinical trials in evaluating the safety of marketed drugs have led to relying on cohort and case-control methods for postmarketing studies. While these latter methods can only indicate an association between a drug and observed conditions, but not that the relationship is causal (49,77), the cumulative experience of multiple cohort and case-control studies that show consistent associations between a drug and a suspected effect can lead to a high degree of confidence that the relationship is causal.

The following three case studies illustrate the use of the four methods of drug evaluation: controlled clinical trials, voluntary reporting, cohort studies, and case-control studies.

CASE STUDIES IN DRUG EVALUATION

Oral contraceptives, the most investigated drugs in use, were first associated with cardiovascular disease in 1966 by British researchers. Earlier that year, they had noticed that Britain's yellow card system had revealed that relatively more reports of thromboembolism (heart attacks, strokes, deep vein thrombosis of the legs with or without emboli to the lungs) were associated with one type of oral contraceptive than with another. A case-control study later that year established that there was a significant association between oral contraceptive use and thromboembolism, but it found no significant difference between the two contraceptive types (38). Publicity over these adverse effects increased voluntary reporting, so that within 3 years more than 1,300 reports of thromboembolism had been received. By 1969, researchers established that it was the total dose of estrogens, not the different types of estrogen, that was responsible for any differences (39). As a result, high-dose estrogen oral contraceptives were removed from the market in 1970. The association between oral contraceptives and thromboembolism has been confirmed in other studies (15,51, 52,73,74).

It is now known that the risk of thromboembolic disease from oral contraceptives increases with age. Young women have a chance of 1 in 20,000 of dying from the cardiovascular effects of oral contraceptives (62); but a woman taking oral contraceptives from age 35 to 45 has a risk of death of about 1 in 1,000 over the 10-year period (32). The risk of heart attack from oral contraceptives has also been found to increase for patients who smoke cigarettes (52), so that older women who smoke have the greatest risk.

Other conditions associated with oral contraceptives include gall bladder disease (6,7), liver tumors (1), yeast infections of the vagina (27), and increased bacteria in the urine (78). Oral contraceptives have also been associated with jaundice, but only in patients with a rare genetic condition in which there is impaired biliary excretion of bilirubin, the Dubin-Johnson syndrome (14). Decreased effectiveness of oral contraceptives has been associated with the use of anticonvulsants and other drugs (54), but oral contraceptives have also been associated with reduced incidences of nonmalignant breast disease (8) and ovarian cysts (58). Most, if not all, of these other conditions associated with oral contraceptive use have been observed in only a few studies, and the role of contraceptives in producing them is not so clear as it is in the case of the occurrence of cardiovascular conditions.

To illustrate that an association between a drug and an observed condition may be too casually inferred, it should be noted that in 1970, a Swedish physician reported Down's syndrome (or trisomy 21, the most obvious symptoms of which are mental deficiency and mongoloid features) in two children whose mothers had taken oral contraceptives before pregnancy. At the same time, one hospital reported increased numbers of children born with the syndrome. Sweden's monitoring system therefore compared the incidence of the syndrome during a period (1968-70) when oral contraceptives were widely used with earlier periods when oral contraceptives were not available. The incidence of the syndrome turned out to be lower in the period of oral contraceptive use (48). The public did not know of the investiga-

tion until it was completed. "One can easily imagine the worldwide alarm such a suspicion could have caused" (3).

Streptokinase, a drug derived from group C beta-hemolytic streptococci for use in dissolving blood clots, was released for marketing in the United States in November 1977, following its use in Europe for many years. Bleeding, allergic reactions, and fever had been found in the premarketing clinical trials carried out on 535 patients. Hoechst-Roussel Pharmaceuticals, manufacturers of the drug, implemented a postmarketing surveillance study at the request of FDA. The study lasted until May 1980, at which time FDA lifted the postmarketing study requirement.

Hoechst-Roussel included a reporting form in each package of the drug vials sent to hospital pharmacies, and requested that the pharmacist have treating physicians complete the forms. Based on sales, the company estimated that reports were returned for about 20 percent of treated patients, a total of 306 patients of 260 physicians in 44 States and the District of Columbia.

Physicians were asked to rate treatment outcomes as "successful," "partially successful," or "unsuccessful." Thirty-nine percent were reported as "successful," 32 percent as "partially successful," and 30 percent as "unsuccessful" (percentages rounded to nearest point).

Fifty percent of the patients (153/306) had a total of 208 adverse reactions, with 49 patients reported to have 2 or 3. The reactions reported were the same as those seen in the clinical trials--allergic reactions, fever, and bleeding. Fifteen patients suffered severe bleeding, and 48 less severe bleeding. Three patients with severe bleeding died, and one had nerve damage secondary to bleeding (femoral hematoma). Most patients recovered from the drug reaction, but a total of 25 of the 306 patients died during or within a few weeks of therapy. The investigators concluded that no adverse reactions were discovered that were not already known from the premarketing clinical trials and that their incidence and severity were similar (71).

This postmarketing study is instructive for a number of reasons. First, it was necessary to select the sample from marketing sources and to rely on voluntary reporting, so there was a bias in patient selection, there were no controls, and the criteria for effectiveness were vague. The low reporting rate of 20 percent is also typical of voluntary methods. Second, the purpose of the study was "to determine whether the incidence and severity of adverse reactions with widespread use would differ from that seen during clinical trials." The investigators concluded that incidence, severity, and type of reaction were similar, but noted that the final sample size was only 306, smaller than that of the 535 patients in the premarketing clinical trials. Adverse reactions with incidences less than those observed in the clinical trials were not likely to be discovered in the smaller postmarketing study. The strongest conclusion that can be reached on the basis of the later study is that the types of drug reactions in an uncontrolled patient population were similar to those of the more carefully selected patients in the clinical trials.

Finally, this study illustrates a problem that is often encountered in evaluating drugs. In contrast to patients taking oral contraceptives, these patients were being treated for underlying diseases, which can complicate the interpretation of what is observed. For example, 25 of the 306 patients died, 15 from pulmonary emboli and 4 from deep vein thrombosis, both conditions that are related to the diseases being treated. The investigators concluded that these deaths occurred about as frequently as they did during the premarketing trials.

Cimetidine, an anti-ulcer drug that blocks the release of stomach acid, was approved for marketing in August 1977. Because it was a new class of therapeutic agent and was expected to be widely used—it was an alternative to surgery in reducing stomach acidity—a postmarketing study was requested of the drug's sponsor—Smith, Kline & French Laboratories. The drug had become available a few years earlier in some other countries, including Great Britain.

The sponsor established a cohort of about 10,000 patients by using its sales representatives to enroll over 1,000 physicians who were asked to complete case report forms on at least 10 patients for whom they would prescribe cimetidine during a 3-month period starting in March 1978.

A second phase (not reported by early 1982) was to cover the following 6-month period. The expected 10,000 patient cohort would provide a 90-percent probability of observing a drug effect with an incidence of 1/4,348 and an 80-percent probability of observing one with an incidence of 1/6,250. The physician response rate was 85 percent, with 9,907 case reports used in the study. A control group was not included because of design and cost problems.

A total of 577 adverse reactions were reported in 442/9,907 (4.4 percent) cases. The investigators concluded that these adverse reactions did not differ in type or incidence from those observed in the premarketing controlled clinical trials (31).

The most common drug reactions observed in the patients were diarrhea and nausea or vomiting. Previous reports in the literature (i.e., spontaneous reporting) from Great Britain had postulated an association between cimetidine use and mental confusion, blood dyscrasias, and endocrine effects. Some patients did develop such symptoms, but the investigators concluded that only the 18 cases of gynecomastia (breast swelling in males) and one case of blood abnormality were related to cimetidine use.

There were 65 patient deaths during the 3-month review period, none considered to be cimetidine-related. Previous spontaneous reports had also led to postulating an association between cimetidine use and stomach cancer (19,34,60,70). However, the hypothesis was viewed with skepticism, as people who have ulcers also have a higher chance of developing stomach cancer. Though the investigators did not address this possible effect of cimetidine, they reported that the 19 patients with tumor-related deaths were diagnosed for corresponding conditions before cimetidine therapy began.

The year after this study was published, British researchers reported experiments in humans on the basis of which they speculated about how cimetidine could produce stomach cancer (59). The investigators pointed out that the toxicological data from long-term studies in rats and dogs did not uncover any evidence of the drug's carcinogenicity, but they contrasted these findings with their experimental findings and with the spontaneous reports associating cimetidine use and stomach cancer in humans.

In contrast to the streptokinase study's enrollment of a smaller cohort than the number of patients evaluated in the premarketing tests, the cimetidine postmarketing study was able to enroll its goal of a cohort of nearly 10,000 patients. The cimetidine postmarketing study, however, is of interest for other reasons.

The published report covering only the first 3 months of cimetidine use found no difference from the premarketing controlled clinical trials in the types or incidences of adverse reactions. One problem with postmarketing studies, however, is to detect adverse reactions without prejudice about what will be found. The findings of the premarketing clinical trials can provide guides for what reactions to anticipate, but such guides might cause the observer to overlook other adverse reactions associated with the drug under study.

In contrast to the published preliminary findings, FDA's review of this study, not yet complete as of early 1982, suggests a lower rate of adverse reactions than that observed in the premarketing trials, although the types of adverse reactions and their relative rates in the two are similar (10). This last observation is in agreement with at least one pharmaceutical company's experience (66):

> Some people might think postmarketing surveillance can sharpen up estimates of incidence of adverse reactions seen in phase III trials. Phase III trials, however, use trained investigators and they ordinarily are treating the more severe patients. Both of these facts contribute to higher adverse reaction rates in phase III studies than one expects to get and actually gets in postmarketing surveillance studies.

Thus, in designing postmarketing studies, the investigator must both be guided by the results of the premarketing clinical trials and not be overly influenced by them.

5.
Current Activities

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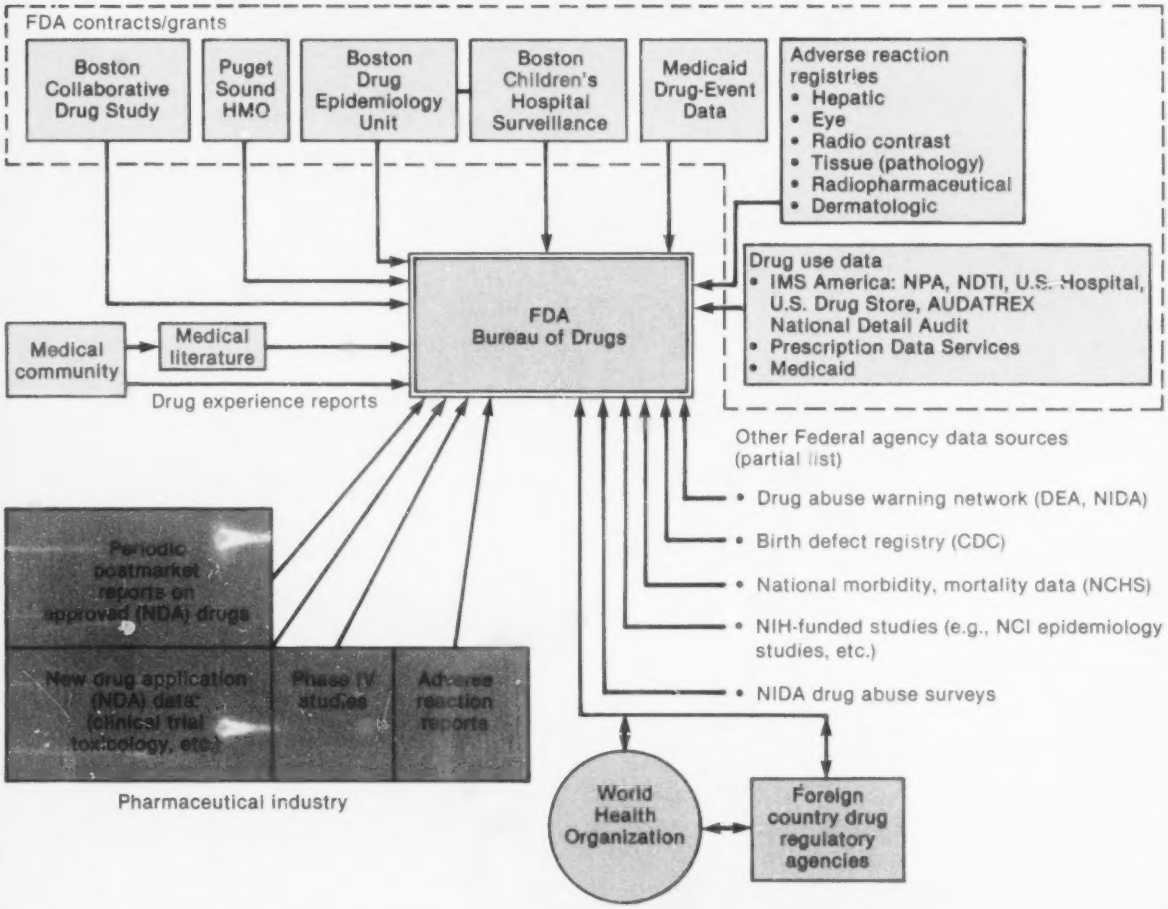
5. Current Activities

The following discussion suggests only some of the kinds of activities and resources that can contribute to postmarketing surveillance.

The Food and Drug Administration (FDA) obtains information on the postmarketing status of drugs from four main sources: 1) pharmaceutical manufacturers, 2) FDA contracts and grants, 3) other governmental agencies, and 4) international centers such as the World Health Organization (WHO). Figure 3 summarizes the data sources available to FDA in its monitoring of drugs.

Pharmaceutical manufacturers are required to report all adverse reactions regardless of whether a causal connection is believed to exist between the drug and the symptom (CFR 21.310.301). Most of these adverse events are reported by physicians, and many manufacturers have routine

Figure 3.—Drug Experience/Epidemiologic Sources Available to FDA for Postmarketing Surveillance and Risk Assessment


FDA contracts/grants
Boston Collaborative Drug Study
Puget Sound HMO
Boston Drug Epidemiology Unit
Boston Children's Hospital Surveillance
Medicaid Drug-Event Data
Adverse reaction registries
• Hepatic
• Eye
• Radio contrast
• Tissue (pathology)
• Radiopharmaceutical
• Dermatologic
Drug use data
• IMS America: NPA, NDTI, U.S. Hospital, U.S. Drug Store, AUDATREX National Detail Audit
• Prescription Data Services
• Medicaid
FDA Bureau of Drugs
Medical community
Medical literature
Drug experience reports
Other Federal agency data sources (partial list)
• Drug abuse warning network (DEA, NIDA)
• Birth defect registry (CDC)
• National morbidity, mortality data (NCHS)
• NIH-funded studies (e.g., NCI epidemiology studies, etc.)
• NIDA drug abuse surveys
Periodic postmarket reports on approved (NDA) drugs
New drug application (NDA) data: (clinical trial toxicology, etc.)
Phase IV studies
Adverse reaction reports
Pharmaceutical industry
World Health Organization
Foreign country drug regulatory agencies

SOURCE: U.S. Food and Drug Administration.

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procedures for responding to such spontaneous reports. A number of companies also carry out "product support studies" to interest physicians in their products, and to defend a drug if it is suspected of causing an adverse effect, or if questions are raised about its therapeutic value (12).

Manufacturers may also have to conduct a "phase IV" postmarketing study as a condition of marketing approval. Two examples of such research, that on streptokinase and cimetidine, were described in chapter 4.

Some manufacturers are also attempting to develop their own surveillance programs. For example, Upjohn used group medical practices to form a pharmacy-based cohort for prospective observational studies of selected drugs in order to establish a large registry of patients to identify and analyze important medical events through follow-up patient questionnaires (5).

FDA grants and contracts cover a number of activities. Voluntary reporting by physicians to medical journals and directly to FDA is augmented by several specialized registries:

- The National Registry of Drug-Induced Ocular Side-Effects collects data from U.S. ophthalmologists on drugs and their effects.
- The Registry of Patients Exposed to Radiopharmaceutical Drugs collects information from a random sample of hospitals licensed to practice nuclear medicine. All patients exposed to radiopharmaceuticals are registered, and adverse effects are reported.
- The Registry of Hepatic Toxicity to Drugs collects data on drug reactions that affect the liver.
- The Registry of Dermatological Reactions to Drugs, administered by the American Academy of Dermatology, was recently initiated to collect data on reactions affecting the skin and on reactions to dermatological drugs.

FDA purchases data from private organizations to estimate the actual population using a drug. One use of this data might be to determine whether patients exposed to a drug have an increased risk of experiencing an adverse effect. Another use might be to estimate the number of patients who would be using a new drug to help decide whether a postmarketing study of the drug would be needed.

For example, FDA's Division of Drug Experience contracted to use the Medicaid Medical Information Systems of Michigan and Minnesota to link individual prescription and diagnostic claim files for 1.2 million patients, to access and tabulate the data, and to provide FDA with online terminal access to the data, to update the patient profiles on a quarterly basis, and to provide specified reports. The Division of Drug Experience plans to use this Medicaid data base for the following purposes: 1) investigation of what FDA considers high-priority issues on adverse reactions, 2) development of data on drug utilization, 3) development of a screening system for hypothesis generation of unsuspected adverse effects, and 4) studies to describe and validate the usefulness of the data base (25). Table 9 summarizes the anticipated uses of this data base. Table 10 identifies this and other data sources available to FDA for estimating actual populations of drug users.

In addition to using the Medicaid data from Michigan and Minnesota to develop cohorts for studies of drug use, FDA contributes to the support of several ongoing surveillance programs, some of which include data collected from other countries (e.g., Great Britain, New Zealand, Israel).

The Boston Collaborative Drug Surveillance Program (44) has accumulated data on the past hospitalizations of more than 50,000 patients. This data base is still useful for evaluating older drugs. The program also uses current data from the 280,000 members of the Group Health Cooperative of Puget Sound (Washington State) and the data files of the Commission on Professional and Hospital Activities-Professional Activity Study in Ann Arbor, Mich. These data sources are useful for evaluating new drugs.

The Drug Epidemiology Unit at the Boston University Medical Center conducts case-control studies (e.g., on birth defects), and also intensively monitors pediatric hospital patients in collaboration with the Children's Hospital Medical Center in Boston.

Table 9.—Potential Uses by FDA of Medicaid Data From Michigan and Minnesota

General description of study	General use	Example	Anticipated future impact
Drug utilization			
1. Overall characterization of drug use by Medicaid population.	Cross-validation with data on drug use.	Oral contraceptive use.	Confirmation of suspected problems (e.g., unlabeled uses).
	Identification of potential high drug exposure problem areas.	Use of isoxsuprine in pregnancy. High codeine use.	Label changes. Publication in medical literature, *ADR Highlights*.
2. Demographics of drug use.	Inappropriate drug use along demographically defined high-risk groups.	Association of high-dose estrogen oral contraceptives with older premenopausal women.	Labeling changes to indicate demographically defined high-risk groups. *ADR Highlights*.
3. Drug use combinations.	Inappropriate use of interacting drugs in individuals.	Use of steroids in individuals on oral hypoglycemic agents.	Labeling changes and publications to warn against untoward drug combinations that appear prevalent. *ADR Highlights*.
4. Drug use in diseased individuals.	Inappropriate use of drugs in certain risk groups defined by disease.	Use of indomethacin in individuals with history of GI bleeding.	Publication to warn of apparent prevalent misuse of drugs. Labeling changes as indicated. *ADR Highlights*.
Drug adverse effects			
1. Relative prevalence/incidence of known adverse effects.	Current rates of ADRs are known only for common drugs—this data base allows definition of relative risk for most ADRs (except rarest)	Relative rate of hepatic disorders in erythromycin (estolate v. other salt users). Relative rate of heart failure in disopyramide v. quinidine or procainamide users (alone and/or in combination).	Labeling changes. Publications (*ADR Highlights* and/or medical literature). General ability to place in perspective ADRs due to disease v. drug.
2. Rate of recognized drug adverse effects.	Supplement to spontaneous reporting system. Source of information on perception and reporting of ADRs.	Estimates of rate of reporting (or physician recognition) of ADRs such as hepatitis, etc.	Also serves as information base for insight into perceived drug-induced disease.
3. Identification of drug adverse effects by means of rate ratios from case control or cohort modules.	Identify possible drug-induced disease for further investigation.	Association of laryngospasm with NSAID.	Stimulate further research using other data bases. Labeling change/warning.
4. Detection of *acute* drug-induced disease from temporal clustering of events following exposure.	Identify possible drug-induced disease for further investigation.	Association of phenylpropanolamine with CVA.	Stimulate further research using other data bases.

SOURCE: U.S. Food and Drug Administration.

Table 10.—Data Sources Available to FDA for Estimating Actual Populations of Drug Users
(current and future)

1. ***IMS America, Ltd.***
   - National Prescription Audit—survey of prescriptions dispensed at pharmacies
   - National Disease and Therapeutic Index—survey of physician-patient contacts listing diagnoses and therapies (not prescriptions)
   - U.S. Hospital—survey of bulk sales to hospitals
   - U.S. Drug Store—survey of sales to drug stores
   - Audatrex—sample of physicians and their prescribing habits over time
2. ***Prescription Card Service*** (PCS)—data on third-party paid prescriptions, usually union, with national estimates
3. ***Medicaid*** (exploratory)—data will be available on all drug use, linked to clinical events, for 1.2 million patients in Michigan and 0.25 million patients in Minnesota

   Other than bulk sales to hospitals, there are no current national samples of hospital drug use.

SOURCE: U.S. Food and Drug Administration.

Other governmental agencies also collect data that may be of use to FDA:

- The National Center for Health Statistics collects a wide variety of health data. FDA has asked the center to collect drug data on death certificates, and also to investigate the possibility of collecting drug information in its National Ambulatory Medical Care Survey.
- The National Centers for Disease Control have a Birth Defects Monitoring Project to alert for possible increases in the incidence of birth defects. This project could help detect birth defects due to drugs taken during pregnancy.
- The National Cancer Institute's Environmental Epidemiology Branch sponsors case-control studies to investigate associations between environmental agents (including drugs)

and the development of specific types of cancer, using data from prepaid health plans.
- The Drug Enforcement Agency and the National Institute on Drug Abuse survey emergency rooms and coroners through their Drug Abuse Warning Network to monitor drugs that are abused and their association with adverse reactions.

International monitoring activities include WHO's Program for International Monitoring of Adverse Reactions, which has 23 participating countries. FDA's Division of Drug Experience is the designated National Monitoring Center for the United States. It exchanges reports with WHO, each organization summarizing the adverse drug reactions (ADRs) added to their systems in the previous year. The purpose of WHO's monitoring program is to increase the probability of detecting effects that might be overlooked by individual countries. Its chief value to the United States is in providing information about drugs that are available elsewhere in the world, but are not yet marketed here.

Drugs may be introduced and used abroad for a number of years before they are approved in the United States. In fact, the more rapid approval and introduction of drugs in other countries has been one of the reasons behind the charge that the U.S. drug approval process is too slow, keeping valuable drugs from the market. However, this earlier introduction of drugs in other countries also uncovers adverse effects and helps modify the indications for use before the drug is released in this country, because the international community can pool and share information on the effectiveness, safety, and use of drugs.

Currently, FDA's Division of Drug Experience receives about 12,000 adverse event reports annually from industry (reports that are mandatory), the medical community, and others. About three-quarters (60 to 80 percent) of these reports come from manufacturers, who, in turn, receive most of their reports from physicians. Table 11 summarizes the sources of adverse event reports for 1972-78, and table 12 identifies individual sources for fiscal year 1978. The relationship between these reported effects and drug use varies greatly. For example, in 1977, approximately 150 reports were on deaths that were "definitely" or "probably" drug related, but more than 400 other reports were not clearly drug related or due to overdoses (63).

The reports of the Division of Drug Experience have been computerized and, depending on their accuracy and completeness, can be screened or retrieved in the following classifications (63):

- by drugs or drug class related to the suspected adverse reactions;
- by adverse reaction related back to suspected drugs;
- by one of four cause-and-effect relationships: definite, probable, possible, and remote;
- by alert "yes" or "no," meaning that the reaction is or is not novel, unanticipated, previously unreported, or not mentioned in the product labeling;
- by demographic data;
- by source of report;
- by possible interactions; and
- by outcome of reaction.
- Retrieval can also extend to original reports on microfilm.

Table 11.—Number and Percentage of FDA's Adverse Event Reports by Source, 1972-78

Source	1972	1973	1974	1975	1976	1977	1978
Manufacturers	9,750	6,700	6,807	8,097	7,664	8,945	9,143
	(76.0%)	(62.2%)	(70.1%)	(75.2%)	(63.8%)	(71.8%)	(81.2%)
Physicians/other health professionals	231	2,189	985	699	2,138	1,862	1,335
	(1.8%)	(20.3%)	(10.1%)	(6.6%)	(17.8%)	(15.0%)	(11.9%)
Hospitals	2,559	1,690	1,306	1,043	1,045	859	423
	(20.0%)	(15.8%)	(13.5%)	(8.7%)	(8.7%)	(6.9%)	(4.0%)
All other	297	182	611	917	1,165	793	358
	(2.2%)	(1.7%)	(6.3%)	(8.5%)	(9.7%)	(6.3%)	(3.7%)
Totals	12,837	10,761	9,709	10,756	12,012	12,459	11,259

SOURCE: A. Ruskin and C. Anello, "The United States of America," in *Monitoring for Drug Safety*, W. H. W. Inman (ed.) (Philadelphia: J. B. Lippincott Co., 1980).

Table 12.—Number of FDA's Adverse Event Reports by Specific Sources, Fiscal Year 1978

Source	Number of reports
Manufacturers	9,143
Physicians/other health professionals:	
Physicians	1,199
Pharmacists	105
Dentists	31
Hospitals:	
Federal	182
Non-Federal	241
All other:	
Consumer	24
District of Columbia	68
Methadone Centers	266

SOURCE: U.S. Food and Drug Administration.

These reports are supplemented by a separate but parallel literature search by FDA of 140 journals (in English) that focuses on serious adverse effects not mentioned in the drug labeling. This literature search is published monthly in FDA's "Current Drug Experience Literature."

FDA has begun to use the computerized file of ADRs in a screening method (screening of adverse reactions, or SOAR) to assist its clinical reviewers in identifying previously unsuspected adverse reactions that might warrant in-depth clinical investigations. The SOAR method compares a drug's proportional share of specific adverse reactions (relative to its therapeutic class) with its respective proportional share of drug use for a particular time period. The latter data are derived from national estimates of the total amount of a particular drug dispensed during a 3-month period, divided by the amount that would be used per day. The resulting number would represent the potential number of days a patient was exposed to the drug. An in-depth review may be considered when the proportional share of reported adverse events relative to the proportional share of drug use is greater than that predicted.

FDA's postmarketing surveillance of ADRs is not a surveillance "system" per se, but rather a group of potentially related activities. Many of these activities are not exclusively carried out for FDA's monitoring program. For example, the intensive monitoring programs to which FDA contributes support also collaborate in large-scale clinical trials of drug efficacy that are sponsored by the National Institutes of Health. Many of the voluntary reporting systems, such as the specialized registries (e.g., those for ocular side effects, dermatological reactions, and hepatic toxicity), also have multiple purposes.

FDA's monitoring is based primarily on voluntary reporting. The agency is just beginning to establish the data bases needed to confirm or reject those possible associations between drugs and adverse reactions that are first identified through the various kinds of voluntary reporting.

These observations point to the following areas of inquiry:

First, how can FDA's coordination of its postmarketing surveillance activities be improved? Currently, it is difficult to evaluate the monitoring activities in which FDA is involved, because their emphasis so far has been on collection of data, not on its final use; thus, the potential uses of the data are largely unrealized.

Second, are FDA's own voluntary reporting and data-gathering programs and the other, more specialized drug reaction registries it supports appropriately targeted and sufficiently utilized? A recent General Accounting Office reevaluation of FDA's voluntary reporting system criticizes FDA's tardiness in evaluating and using these reports (29). The relative value of the various specialized registries to FDA's monitoring responsibilities is not known.

Finally, should FDA be responsible for testing the hypothesis that a drug may be associated with an adverse reaction, or should that be the responsibility of the drug's manufacturer? FDA could support the formation of various prospective cohorts and coordinate that activity with the information FDA receives from voluntary reporting. But FDA's role could also be limited to helping identify the most important drugs to monitor, with the actual monitoring performed by the drug's manufacturers.

6.
Issues and Options

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6. Issues and Options

Current interest in prescription drug evaluation and monitoring is focused on the premarketing approval process, while postmarketing surveillance has waned as a policy issue. The recommendations of the Joint Commission on Prescription Drug Use, issued in January 1980, have not been implemented, and the linchpin of its recommendations, a national Center for Drug Surveillance, reached its zenith before the commission issued its report when the center concept (renamed as the "National Center for Drug Science") was included in the 1979 bill that passed the Senate but was not acted on by the House of Representatives. In contrast, in the first session of the 97th Congress, the Senate passed the Patent Term Restoration Act of 1981, in large part as a direct response to the length of the drug approval process. As mentioned earlier, the House of Representatives also voted on the bill, but under suspension of its rules. Although the bill received a majority of the votes, a two-thirds vote was required for passage under such conditions, and the bill fell just short of the two-thirds majority needed. Shortly prior to publication of this report, the report of the Commission on the Federal Drug Approval Process and the current Food and Drug Administration (FDA) review will both also be complete. Both focus on methods to hasten drug approval by FDA.

Thus, policy formulation and implementation for the premarketing approval process is being pursued without parallel efforts for the postmarketing period. As one person has remarked (43):

> I don't really see that any significant shortening of approval time can be engaged in as a result of a tradeoff in regard to postmarketing surveillance, although this was originally thought to be a possibility when a former FDA commissioner suggested that such was the case.

Others do see a linkage between the approval process and postmarketing surveillance, although they agree that there are no direct tradeoffs in the kinds of information obtained (4):

> Postmarketing evaluation studies can be conducted much more cheaply than clinical trials . . . As a motivator for industry, it is desirable to have the drug marketed sooner with a return on investment while studies are being conducted. At the same time, much larger observational studies can be done, at the same cost, [to] evaluate drugs in their customary use situation. It is important to recognize that phase III clinical trials and postmarketing drug evaluation studies are not alternatives. They address different issues and are complementary. The appropriate question is whether it would not be better to reduce the size and cost of phase III with limited likelihood of losing meaningful information and conduct much larger studies after marketing.

Hence, some relationship does exist between proposed changes in the premarketing approval process and the monitoring activities of the postmarketing period. This relationship can be clarified by the answers to two questions. Can the size and cost of phase III clinical trials be reduced with limited likelihood of losing meaningful information? And, should pharmaceutical manufacturers be required to maintain the level of their drug evaluation responsibilities by increasing postmarketing surveillance?

Issue 1:

Revising premarketing tests and shortening the drug approval process.

The efficacy and safety tests in animals and humans specified in FDA regulations for premarketing approval are based on broad statutory language (21 U.S.C., sec. 355 (d)). "Adequate tests by all methods reasonably applicable" are necessary to show that a drug is safe for use. There must also be "substantial evidence that the drug will have the effect it purports or is represented to have," where "substantial evidence" is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific

training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have."

Efforts to shorten the drug approval process have focused not on the statutory language but on the regulations issued by FDA to implement the law. Thus, the focus here is on oversight issues, not on legislative changes.

Proposals to curtail or eliminate phase III premarketing tests, or shift them to the postmarketing period can be evaluated both theoretically and experientially.

Theoretically, phase III testing is significantly more sensitive than phase II testing. Adverse effects with an incidence of 1/100 or more are more likely than not to be detected in the 100 to 200 patients in phase II. But the theoretical sensitivity of detection rises in phase III to 1/500 with 500 patients, and 1/1,000 with 1,000 to 3,000 patients (see ch. 4, table 5).

These observations are relevant to the detection of adverse reactions, but they are not so relevant to the detection of therapeutic effects. A drug that helps only 1 in 100 patients would not be very effective, so effectiveness should be established in phase II. Phase III is intended to gather additional evidence on a drug's effectiveness for specific indications.

If phase III testing were curtailed or eliminated, there is also the question of whether premarketing evaluations would test sufficient numbers of patients to reasonably ensure a drug's safety or give substantial evidence of its efficacy. Even under current regulations, the use of a drug on humans is very limited before the drug is released for market: 20 to 80 patients in phase I; 100 to 200 patients in phase II; and 500 to 3,000 patients in phase III—a range of only 620 to 3,280 patients per drug (excluding controls). Curtailing the larger phase III tests would lower the range of patients tested to 620 to 780, and eliminating phase III tests altogether would reduce that range further to 120 to 280 patients who would be tested with a drug before it is released for general use.

In addition to theoretical criteria, **experiential criteria could be applied in considering proposals to curtail or eliminate phase III tests.** The diminished power to observe adverse drug effects that such changes theoretically entail may not in fact be found, or if it is, it may concern only infrequent minor effects. As was mentioned previously, FDA is reviewing past phase III tests to see if the trials for chronic effects or those with large sample sizes have contributed useful information beyond that obtained in phase II and early phase III. This review should indicate whether or not actual experience reflects the theoretical differences discussed above between phase II and phase III tests involving 500 versus 1,500 to 3,000 patients. Agreement of the experiential data with the differences theoretically predicted would strengthen the hypothesis that curtailing phase III tests would lower the capacity of current premarketing tests to identify adverse reactions. If the experiential data fail to reflect the theoretical differences, then a better case can be made for curtailing phase III, with or without transfer of some of its testing to the postmarketing period.

Current interpretations of the statutory requirements for "adequate tests" of safety and "substantial evidence" of effectiveness emphasize methodology, as reflected in the requirement that each indication for which a drug is intended be supported by at least two well-controlled clinical trials. This is the reason for the preceding discussion of statistical guidelines and the complementarity of normative guidelines in evaluating how FDA revises its drug approval regulations and procedures. **But FDA can alter the criteria by which it approves drugs.** For example, propanolol, the first beta-blocking drug approved for use in the United States, was approved by an advisory committee on the basis of all the evidence presented to FDA, even though no one study was found to be adequate and well controlled (21). And in late 1981, timolol, another beta-blocker, was approved for use in preventing death and recurrent heart attacks in patients who have survived initial heart attacks. This approval was based on a foreign study—a 3-year Norwegian study showing that the risk of death or a second heart attack following a first heart attack was

reduced by about one-third when timolol therapy began within 28 days and continued for up to 33 months (26). Although the study was Norwegian, the results were accepted for publication by the most prestigious medical journal in the United States, the *New England Journal of Medicine* (57). (Approval for another indication, high blood pressure, was based on U.S. studies.)

Approval of timolol may also have been influenced by a similar study of propanolol in the United States by the National Heart, Lung, and Blood Institute (NHLBI). In the clinical trial of propanolol, NHLBI's Policy and Data Monitoring Board took the unusual step of curtailing the trial when data indicated that patients receiving propanolol experienced a 26 percent lower mortality from all causes than did a control group. According to the Beta-Blocker Heart Attack Study Group (2):

> The results . . . strengthen and extend the conclusions of previous studies of beta-blockers in survivors of acute myocardial infarction. This large study of a noncardioselective agent is in accord with the results of the recent trial of timolol maleate.

The criteria for FDA's acceptance of timolol, therefore, closely approximated the requirement of two well-controlled clinical trials, notwithstanding the fact that one of these trials was performed in another country.

The approval of propanolol and timolol, however, do illustrate that FDA can grant exceptions to its usual requirement of two well-controlled U.S.-based clinical trials. In the case of timolol, the validity of the Norwegian study was confirmed by its acceptance for publication in a prestigious U.S. medical journal, and even though approval was based on this one study, the results of the NHLBI trial on propanolol, another beta-blocker, must surely have influenced the FDA decision to approve timolol for prevention of heart attacks. In the case of propanolol, the first beta-blocker drug to be approved by FDA, approval was based on the preponderance of the evidence as judged by an advisory committee.

In such a case, expert judgment relies on qualitative, not quantitative, criteria in approving a drug, and such an approach falls outside the theoretical and experiential guidelines outlined above. **If FDA is to rely increasingly on such qualitative criteria through the increased use of advisory committees, it will be necessary for FDA to develop general guidelines to aid the advisory committees in their deliberations.** Otherwise, in a case-by-case approach, evidence of the same quality may lead to approval for one drug and nonapproval for another.

Issue 2:

Improving postmarketing surveillance and its role in the drug approval process.

Controlled clinical trials, the most accepted scientific means of identifying and confirming a drug's effectiveness and safety, are used in drug testing in the premarketing stage, but the evidence they yield is necessarily limited because their sample sizes are small and the patients they test represent only a fraction of the kinds of patients who will eventually use the drug. Other shortcomings of small controlled clinical trials are that rare but serious adverse effects or effects with a long latency will not be observed, and that average conditions of use are not duplicated. These limitations of premarketing testing can only be addressed in the wider use that comes with marketing the drug. Thus, **even if phase III testing were not curtailed or eliminated, FDA's powers in the postmarketing period could be strengthened to enhance its surveillance role.**

Generally, postmarketing surveillance "systems" that have been advocated are not systems in the formal sense, but a series of related activities oriented toward several purposes, with the regulatory approval process being only one use. The activities most frequently mentioned include the following three.

First is the building of a resource base through training of additional experts and improving epidemiological tools such as methods for case-control and cohort studies. The concept of a national Center for Drug Surveillance, advocated in the report of the Joint Commission on Prescription Drug Use, was one such attempt. Others believe, in contrast, that the resources are already in hand. According to Jick (40):

> Contrary to the views stated in the report [of the Joint Commission on Prescription Drug Use], I believe that methods to efficiently perform postmarketing surveillance are known and well tested, and that a vast amount of data has already been collected to evaluate drug toxicity.

Remington states (61):

> [M]ethods for estimating characteristics of large populations, although available since the 1940's, have not been assimilated to any appreciable extent into the field of drug evaluation . . . I think we must begin to apply modern mass population methods to modern problems of drug evaluation, both at the pre- and post-marketing levels. Such methods, however, are particularly appropriate to the evaluation of marketed drugs.

Second is strengthening voluntary reporting to identify possible adverse drug reactions. Once such reactions are suspected, clinical trials, case-control, and cohort studies could be used to determine whether an association with drug use in fact exists. In this regard, FDA has come under criticism insofar as its adverse drug reaction reporting activities are concerned. For example, the activities listed in chapter 4 have been criticized as being little more than a catalog, with no assessment of the relative values of the various activities (80). Furthermore, in a recently released followup to a study conducted in 1974, the U.S. General Accounting Office concluded (29):

> Many adverse reaction reports do not get to the Division maintaining the system and many others require a long time to get into the system. Some of the missing or late reports involved serious reactions which were not discussed in the drug labeling. Reporting by non-manufacturer sources, such as hospitals or physicians, could also be increased.

Third is developing an efficient method for monitoring selected drugs after their release into the market. The most frequently mentioned mechanism is formation of prospective cohorts of drug users, utilizing existing data bases such as those previously identified, i.e., Medicaid, Medicare, the military health systems, and some health maintenance organizations. In the opinion of one expert, appropriate large-scale systems are available, but only drug companies currently use them (41).

These components of a postmarketing surveillance "system," and FDA's role in supporting and using them, are oversight issues.

There are also several legislative options that could strengthen FDA's powers in the postmarketing period. The following legislative options are presented for congressional consideration.

Option 1: Give FDA the power to require postmarketing studies.

Currently, FDA has no express power to require a drug's sponsor to conduct postmarketing studies of the types summarized earlier under "phase IV" testing. Drug companies have agreed to such requests in the past, however, because refusal might mean nonapproval of the drug.

FDA is examining these studies to see if they provided the kinds of information identified in its objectives for "phase IV" testing. Additional questions are to determine when adverse reactions became specified on the package insert, and whether the source of the identification of adverse reactions was spontaneous reports, the postmarketing study, or both.

However, a broader analysis is needed, one that does not focus only on these specific studies. It would be helpful if FDA also assessed a sample of drugs that have been marketed for several years to see if significant additional adverse reactions were later discovered that were not uncovered during premarketing trials. Or a study could be conducted on the significant adverse events that were discovered during the postmarketing period. In either of these latter types of studies, the assessment focus should be on whether the adverse effects could have been discovered through studies of the kinds performed by the manufacturers at FDA's request. This assessment could provide additional information for deciding whether formal postmarketing monitoring would be valuable.

The larger postmarketing studies carried out by manufacturers at the request of FDA have cost $1 million to $3 million each (11), and the industry is certain to resist giving FDA explicit authority to require them. Industry might be more willing to conduct postmarketing studies if the drug approval process were shortened, however, since it

could obtain a quicker return on its investments. In the absence of such a tradeoff, Congress could consider increasing FDA's appropriations to finance selected postmarketing studies on a drug-by-drug basis.

A variation of this option is for FDA to use its existing regulatory powers over advertising and promotional practices to "certify" an industry-sponsored postmarketing study. Although initially reluctant to conduct postmarketing studies, the industry now sees them as part of its marketing strategy. Physicians may cease to cooperate, however, if they feel they have been used to promote a company's product. FDA certification could be used to distinguish between postmarketing monitoring and "product support studies" that are used to interest physicians in a manufacturer's products and to defend a drug's safety and therapeutic value (69).

Option 2: Give FDA the power to restrict the distribution, dispensing, and administration of a drug.

FDA has considerable power in withholding approval for a drug, but once a drug is approved, there is a significant shift in the burden of proof and in the amount of evidence required to rescind approval. If FDA had the authority to restrict drug marketing or less burden of proof in rescinding approval, it might give approval more freely in the first place. Restrictions on drug use and a lesser burden of proof for FDA to rescind approval would be particularly pertinent in the first several years of marketing, when adverse effects are still quite likely to be identified. The therapeutic-toxic ratio of some new drugs is so narrow that it seems reasonable to provide the means whereby FDA can restrict the use of certain prescription drugs to groups of specially trained or experienced physicians.

S. 1075, the bill introduced in 1979 and passed by the Senate, would have given restrictive powers to FDA, provided that: 1) the drug presented significant risks to patients or the public health; 2) a drug could not be determined to be safe unless restrictions on distribution and dispensing were imposed; 3) the restrictions could reasonably be expected to reduce the risks while permitting its use in appropriate patients; and 4) no other administrative or educational actions permissible under the law could reasonably be expected to reduce the risks. The bill also would have allowed a drug to be restricted to practitioners with special training or experience in its use or to practitioners for use in certain facilities, but only if this were necessary to determine drug safety; and no practitioners could be excluded solely on the basis that they were not eligible for certification in a medical specialty. The 1979 Senate bill also would have required FDA to review any imposed restrictions every 2 years.

The Medical Device Amendments of 1976 (Public Law 94-295) contains somewhat similar language in its section on "restricted devices." According to this amendment, a device could be restricted in its sale, distribution, or use if, "because of its potentiality for harmful effect or the collateral measures necessary to its use, the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness." The law also contains a prohibition against excluding practitioners solely because of their ineligibility for certification in a medical specialty (21 U.S.C., sec. 360j(e)).

In a limited or phased distribution, drugs could be introduced into different geographic regions rather than into the whole country at once. The regions could be chosen with attention to the fact that some drugs are used more in one part of the country than another. Introduction of drugs on a regional basis could also provide some insurance against unexpected adverse effects in that less of our population would be at risk, but different regions could be used for the first marketing of different drugs so that no one region would be the "guinea pig." By specifying the regions well, comparable regions could be compared for reported side effects (55).

A variation of this option is to develop a parallel approval process for the use of a limited group of drugs during phase III testing. This special phase III testing would be considered only as a relatively exceptional procedure restricted to drugs of unusual need and promise. For drugs of apparent unusual therapeutic value compared with alternative therapies and with acceptable risk, a limited number of physicians could be permitted

to use a drug without the fully detailed record-keeping requirements of phase III (28).

Option 3: Change the standard for a drug's removal from the market from "imminent hazard to the public health" to "unreasonable risk of illness or injury to any segment of the population" or some other less stringent standard.

Such a change was contained in the 1979 Senate bill. However, under the present law, the "imminent hazard" standard is to be used only in cases where a drug's harmful effect would be so immediate and severe as to justify suspension of due process until after the drug has been removed from the market. The "imminent hazard" standard applies only to cases where FDA suspends approval of a drug first, then gives the drug sponsor prompt notice and an opportunity for an expedited hearing. FDA otherwise can remove a drug from the market on the basis of new evidence on safety or effectiveness or for other reasons such as discovering that approval of the drug was based on an untrue statement of a material fact. To take such action, however, FDA must give due notice and an opportunity for a hearing before it can proceed.

Substituting "unreasonable risk" for "imminent hazard" in the standard would blur the present distinction between those cases when due notice and opportunity for a hearing should be required before a drug could be taken off the market and those cases when it would be justified to remove a drug from the market prior to notice and an opportunity for a hearing. In other words, "unreasonable risk" is already the standard for those cases when, in order to protect the drug sponsor's economic interests, FDA must give due notice and an opportunity for a hearing before taking action. If such a change in the standard were approved, FDA would be able to remove a drug for any of the currently accepted reasons to question safety without first giving notice and an opportunity for a hearing.

In the Medical Device Amendments of 1976, no such "imminent hazard" standard is specified. There is, however, a slight difference in the wording of the law. It states that, if a drug does not represent an "imminent hazard," withdrawal of the drug's approval can proceed "after due notice and opportunity for a hearing" (21 U.S.C., sec. 355(e)). For devices, withdrawal of approval can proceed "after due notice and opportunity for **informal** hearing" (emphasis added) (21 U.S.C., sec. 360(e)).

In sum, efforts to shorten the drug approval process in the premarketing period could take place through reinterpreting the guidelines for assessing safety and efficacy. This report has provided theoretical and experiential criteria for evaluating how such changes could affect the detection capabilities of the current guidelines. It has also discussed the desirability of guidelines for the kinds of qualitative changes FDA is implementing regarding the evidence required for drug approval. These changes include accepting foreign data and cumulative evidence (as opposed to the requirement of at least two well-controlled clinical trials). Finally, the report has identified options relating to FDA's postmarketing surveillance. These options could be pursued independently of any revisions in the premarketing drug approval process, but they could also be implemented to require drug sponsors to maintain their level of drug evaluation responsibilities if there is a change in current premarketing approval requirements.

Appendixes

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Appendix A.—Selected Excerpts From the Statutes Governing Drugs and Medical Devices

Drugs

Grounds for refusing application; approval of application; "substantial evidence" defined (21 U.S.C., sec. 355(d)).

If the Secretary finds after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; (5) evaluated on the basis of the information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health (21 U.S.C., sec. 355(e)).

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j) of this section or to comply with the notice requirements of section 360(j)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsec-

tion; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

Devices

Restricted devices (21 U.S.C., sec. 360j(e)).

The Secretary may by regulation require that a device be restricted to sale, distribution, or use—

(A) only upon the written or oral authorization of a practitioner licensed by law to administer or use such devices, or

(B) upon such other conditions as the Secretary may prescribe in such regulation, if, because of its potentiality for harmful effect or the collateral measures necessary to its use, the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness. No condition prescribed under subparagraph (B) may restrict the use of a device to persons with specific training or experience in its use or to persons for use in certain facilities unless the Secretary determines that such a restriction is required for the safe and effective use of the device. No such condition may exclude a person from using a device solely because the person does not have the training or experience to make him eligible for certification by a certifying board recognized by the American Board of Medical Specialties or has not been certified by such a Board. A device subject to a regulation under this subsection is a restricted device.

Withdrawal of approval of application for premarket approval (21 U.S.C., sec. 360e(e)).

The Secretary shall, upon obtaining, where appropriate, advice on scientific matters from a panel or panels under section 360c of this title, and after due notice and opportunity for informal hearing to the holder of an approved application for a device, issue an order withdrawing approval of the application if the Secretary finds—

(A) that such device is unsafe or ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof;

(B) on the basis of new information before him with respect to such device, evaluated together with the evidence available to him when the application was approved, that there is a lack of a showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling thereof;

(C) that the application contained or was accompanied by an untrue statement of a material fact;

(D) that the application (i) has failed to establish a system for maintaining records, or has repeatedly or deliberately failed to maintain records or to make reports, required by an applicable regulation under section 360i(a) of this title, (ii) has refused to permit access to, or copying or verification of, such records as required by section 374 of this title, or (iii) has not complied with the requirements of section 360 of this title;

(E) on the basis of new information before him with respect to such device, evaluated together with the evidence before him when the application was approved, that the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or installation of such device do not conform with the requirements of section 360j(f) of this title and were not brought into conformity with such requirements within a reasonable time after receipt of written notice from the Secretary of nonconformity;

(F) on the basis of new information before him, evaluated together with the evidence before him when the application was approved, that the labeling of such device, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary of such fact; or

(G) on the basis of new information before him, evaluated together with the evidence before him when the application was approved, that such device is not shown to conform in all respects to a performance standard which is in effect under section 360d of this title compliance with which was a condition of approval of the application and that there is a lack of adequate information to justify the deviation from such standard.

Appendix B.—Conclusions and Recommendations of the Joint Commission on Prescription Drug Use, Jan. 23, 1980

1. Postmarketing surveillance (PMS) can be used to develop information about prescription drugs that is unavailable from premarketing studies but necessary and/or useful for the clinical practice of medicine or ongoing regulation of drugs. Existing postmarketing surveillance programs should be coordinated with new programs to form a comprehensive system.

2. The purpose of postmarketing surveillance is to detect important drug effects earlier than would otherwise be possible. The surveillance, per se, or its results will not and cannot be used to change the biological properties or effects of drugs, but they can be used to minimize the harmful consequences and maximize the optimal use of drugs.

3. Certain risks posed by a PMS system must be recognized, accepted, and addressed, although they are judged by the Commission to be far outweighed by potential benefits.

4. Highest priority in a PMS system should be given to surveillance of new chemical entity prescription drugs, delayed or slowly developing drug effects, commonly used drugs, populations in which drug effects are not well documented, certain important medical events (e.g., births, deaths, etc.) and their relationship to drug use, and patterns of prescription drug use. Other, but secondary, priorities should include the study of: certain important non-prescription drugs, the drug-taking practices of patients, the frequency of given drug effects, dose-response relationships, the characteristics of patients who experience certain effects as compared to those who do not, the relative risks and benefits of individual drugs, changes in frequencies of drug effects over the course of time, and the comparative efficacy and safety of different drugs within the same class.

5. PMS must operate, to the maximum extent possible, in a setting of actual medical practice. In the majority of instances, PMS should be concerned primarily with drugs marketed without special restrictions beyond those already enforced for drugs of certain classes. Data collection for PMS should not interfere with the normal delivery of health care.

6. A PMS system will require both an alerting (hypothesis-generating) mechanism and a confirming or rejecting (hypothesis-testing) mechanism. Hypotheses must be recognized as *suggestions* about cause-effect relationships and not as established fact.

7. An hypothesis-generating mechanism should ideally have access to all animal and clinical data about a drug.

8. A great deal of selectivity will be required for judicious decisions about which of the available hypotheses to test.

9. PMS must insure that great attention is paid to research design and to the sequence of studies. Particular attention should be paid to the validity of the methodology and to the sample size required. Possible types of study are prospective or retrospective, experimental or non-experimental, controlled or uncontrolled, cohort or case-control, studies of drugs or of events, and studies of prophylactic, therapeutic, or diagnostic drugs.

10. Development of new methodology for study of drug effects must be a high priority for the PMS system.

11. The drug effects requiring study will be expected toxicity, unexpected toxicity, intended efficacy and unintended efficacy.

12. Currently available methodology can be used to study expected or unexpected toxicity and unintended efficacy, successfully detectng events that occur with a frequency of at least one event per 1000 exposures. Less frequent events (e.g., one in 10,000 uses) can be detected less reliably.

13. The Commission strongly recommends against PMS that ignores the determination of intended efficacy and of long-term drug effects.

14. An intensive system of surveying the medical literature should be established and particular attention given to a systematic review of data comparing drug responses in various countries.

15. A PMS system should develop methods of seeking and receiving brief reports from large numbers of health professionals.

16. Prospective, non-experimental cohorts that are long-term and lifelong, if possible, should be established for PMS studies.

17. Liaison between the various components of a PMS system will be necessary. This would require development of a standardized terminology for describing PMS and for use in PMS.

18. Reports must be prepared, published and distributed to all parties involved in or affected by PMS. Multiple types of reports will be necessary, tailored to the differing needs and interests of the recipients.

19. For a prescription drug surveillance system to

be effective, it must have the confidence of the public at large, including health care providers and patients. This confidence must extend not only to the validity of the information generated, but also to the manner in which the information will be used.

20. In order to maintain trade secret protection for manufacturers without prejudicing the PMS system's public and academic accountability, only the FDA should have the power to require the disclosure of such secrets. Because of this restriction, the FDA must assume responsibility for reviewing this trade secret data for any hints of drug effects in man that it may contain.

21. In order to protect patient confidentiality, individually identifiable information should be kept strictly confidential by any PMS system unless patients specifically authorize release, with only the following exceptions:

a. Such information could be released to organizations engaged in similar research if an express finding with supporting written statements is prepared documenting that such disclosure is necessary and identifying the individual receiving the information. Such organizations must have comparable guarantees of confidentiality as the organization releasing the data. Redisclosure by the receiving organization would be prohibited without written approval of the original organization.
b. Disclosure could be made to a properly identified recipient pursuant to a bona fide medical emergency.
c. Both patient and provider must have access to their own identifiable data and the ability to make corrections or amendments.

22. Given the fact that the law is developing on the issue of provider liability for disclosing patient identifiable medical records, the Commission recommends that the organizations concerned with PMS review the issue of liability as they begin to undertake PMS functions.

23. In order to assure adequate security for data gathered, a PMS organization should:

a. Maintain only that information which is relevant and necessary to accomplish the purpose.
b Maintain all records used in making any decisions about an individual with such accuracy, relevance, timeliness, and completeness as is reasonably necessary to assure fairness to the individual in the determination.
c. Establish administrative, technical, and physical safeguards to insure the security and confidentiality of records.

24. The value for PMS of a limited shield law is recognized. Such a law would specify that identifiable information of the patient or provider submitted voluntarily to a PMS organization could not be admissible as evidence in a medical or product liability action, and might remove a deterrent to voluntary reporting. Even without such a law however, the PMS functions of the CDS [Center for Drug Surveillance] should commence and the results should be used to define whether evidence needs to be gathered to support the need for and formation of shield law in order to have an optimal PMS system.

25. A national Center for Drug Surveillance (CDS) is necessary in the United States.

26. The objectives and functions of the CDS should be to educate scientists, prescribers and the public, to perform and encourage research into drug effects and to promote cooperation among all existing PMS programs.

27. In using its resources, the CDS must be strictly accountable for fairness, scientific accuracy, and honesty.

28. The activities of the Center for Drug Surveillance (CDS) should not unnecessarily duplicate the functions of other organizations engaged in PMS activities, whether public or private.

29. The CDS should be a private, non-profit, non-regulatory organization with a full-time staff and a physical facility located in an environment that can support and be supported by academic endeavors.

30. After five years, there should be an external review of the effectiveness of the CDS. If the projected benefits from the CDS are not realized, the CDS should be abandoned.

31. Support for the CDS should be in addition to, not instead of, added support for other worthwhile PMS activities.

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